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BONE AND JOINT LESIONS OF YAWS WITH X-RAY FINDINGS IN TWENTY CASES [1]

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SEVEN PLATES

While attending the clinical course of instruction of the graduate school of tropical medicine and public health of the College of Medicine and Surgery, University of the Philippines, during the 1916 session, my attention was directed to the study of the painful bone and joint involvements occurring in some cases of yaws. This complaint prevailed among a great number of patients that were subsequently seen in the barrios of Las Piñas and Parañaque.

Through the courtesies of Doctors Luis Guerrero, Domingo, and Argüelles arrangements were perfected by which a group of one hundred cases of yaws was collected for study.

My work was confined to the cases suffering from bone or joint lesions. Any one who has attempted such a work among Filipinos realizes that there are certain limitations in obtaining reliable information that might materially affect one's conclusions. The first month of the work was spent in gaining the confidence of the patients by frequent visits to their homes, by furnishing free medicine, and by assuring them of no inconvenience and of a cure of the disease.

The diagnoses of these cases were made by the histories, by the clinical symptoms and manifestations, and by the demonstration of *Treponema pertenue* under the dark-field microscope

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in the cases where an open lesion was present, and by a careful history of those without open lesions, so as to remove any doubt as to the diagnosis.

Twenty per cent of the cases of this group of patients, as they presented themselves for treatment, suffered from bone or joint lesions. These patients were persuaded to come to the Department Hospital, Manila, for X-ray pictures and treatment. A röntgenological survey of all the bones of the body was made of each case, regardless of whether or not the patient complained of pain in the part X-rayed. Subsequent X-ray pictures were made, in order to follow the progress of the lesions under treatment.

In the majority of cases the lesions show as rarefied areas, irregularly oval or elliptical in shape with the long axis parallel to that of the bone in which the lesions are located. The size varies from the smallest discernible area to one that is two or three centimeters in length. The rarefication presents moderately well-defined borders separating it from the unaffected bone and varies in translucency from the slightest differentiation of unnatural transparency to one simulating a perforation. Most of the lesions appear to originate in the interior of the bone, while a number can be seen as small excavations on its outer surface. When the lesion is on the surface of the bone, the periosteum is usually destroyed, but occasionally the cortex shows thickening, and the periosteum is separated from the bone. In two cases of this series there is a general thinning of the cortex of the bone and a loss of the cancellous-tissue appearance. About two per cent of the cases show a nodular type of lesion, evidenced by swelling over the surface of the bone, with a localized thickening of the cortex, which sooner or later in the course of the disease shows rarefication in its center.

In the chronic lesions marked irregularity of the bony outline is evident, and the picture characteristic of the earlier lesions is more or less lost. The bone as a whole becomes deformed, and the growth of the bone is interfered with both in length and breadth. This dwarflike picture is most frequently noticed in the cases showing the lesions in the epiphyses. Within the joints the destruction is most frequently seen on the parts of the articular surfaces most exposed to trauma, as oval or irregularly shaped excavations, making the outline of the articular surface rough and uneven. It is concluded from this series of cases that the joint pains complained of are due in most part to the presence of the lesions on the articular surfaces.

With the exception of the 2 per cent of cases showing as a swelling over the surface of the bone, the X-ray picture is different from the bone lesion of syphilis, in that: (1) The periosteal proliferation is absent, and (2) the thickening of the cortex of the bone is absent. Also, in the 2 per cent of cases where thickening of the cortex is present, the thickening remains localized, does not tend to extend along the whole length of the bone, and sooner or later shows rarefication in the center of the lesion.

The bone lesion of yaws may simulate (1) tuberculous or septic central abscess, (2) gumma, (3) hydatic cyst, (4) benign cyst, (5) fibrous osteitis, (6) enchondroma, (7) endothelioma, (8) secondary carcinoma, (9) myeloma, and (10) sarcoma. The differential diagnosis can be made only by combining the radiographic appearances with all clinical data, including the history, physical signs, and evidence of disease or tumor in other parts of the body.

Summarizing the findings in Table I, it is seen that in 20 cases of bone lesions in yaws:

1. The shaft of the bone is the most frequent location of the lesion and shows involvement in 80 per cent of the cases.
2. The epiphyses or articular surfaces are involved in 20 per cent of the cases.
3. The tibia is the bone most frequently involved (40 per cent of this series).
4. The order of frequency of occurrence of the lesions in the other bones is as follows:
   - (*a*) Tarsal bones, 40 per cent (75 per cent of these lesions occur in the os calcis).
   - (*b*) Fibula, 35 per cent.
   - (*c*) Phalanges of feet and hands, each 30 per cent.
   - (*d*) Metatarsal bones, metacarpal bones, and radius, each 20 per cent.
   - (*e*) Patella and humerus, each 15 per cent.
   - (*f*) Femur and ulna, each 10 per cent.
   - (*g*) Carpal bones, ribs, sternum, and pelvic bones, each 5 per cent.
   - (*h*) In the bones not mentioned no lesions were found.
5. There is no constant relation of the location of the external lesion to the bone lesion.
6. The order of frequency of occurrence of the lesions in the joints is as follows: Knee, finger, ankle, and elbow.
7. The lesions are multiple in 75 per cent of the cases, the greatest number being one hundred thirteen.
8. The time between the appearance of the primary lesion and bone lesions varies from six months to nine years, with an average of two and eight-tenths years. In this series 45 per cent of the cases showed bone lesions one year; 15 per cent, two years; 5 per cent, three years; 10 per cent, four years; 5 per cent, five years; 15 per cent, six years; and 5 per cent, nine years after the appearance of the mother yaw.

TABLE I.—*Site of lesion, bones involved, interval between appearance of primary and bone lesions, and ages of patients in twenty cases of yaws.*[a]

	Case No.																			Total.
	1	2	3	4	5	6	7	8	9	10	11	12	20	21	22	23	24	25	30	31	
Phalanges of hand	1		1			1		1										1		1	6
Metacarpus	1		1					1							1						4
Carpus			1																		1
Ulna			1					1													2
Radius	1		1				1	1													4
Humerus			1					1											1		3
Scapula	1																				1
Sternum																1					1
Clavicle																					0
Ribs			1																		1
Vertebra																					0
Pelvic bones			1																		1
Femur			1					1													2
Tibia	1		1		1	1		1				1		1	1						8
Fibula	1	1	1					1						1	1			1			7
Patella	1		1					1													3
Tarsus			1												1						2
Os calcis		1			1				1				1		1		1				6
Metatarsus	1		1	1								1									4
Phalanges of feet	1		1				1	1		1	1										6
Shaft	1	1	1	1	1	1	1	1		1	1	1		1	1			1	1	1	16
Epiphyses	1		1					1							1						4
Total lesions	19	5	52	2	2	10	8	113	1	1	2	2	2	6	18	1	1	2	1	2	

Appearance of primary lesion	1909	1915	1911	1915	1914	1915	1911	1916*	1911	1915	1909	1916	1912	1912	1905	1905	1910	1913	1910	1915	------
Appearance of bone lesion	1910	1916	1912	1916	1916	1916	1912	1916	1914	1917	1915	1917	1916	1917	1914	1907	1916	1917	1916	1916	------
Years between appearance of primary and bone lesions	1	1	1	1	2	1	1	½	3	2	6	1	4	5	9	2	6	4	6	1	[b]2.8
Age ---------- years	7	10	15	7	23	50	28	27	16	7	36	7	15	17	14	18	14	5	19	8	------

[a] Each individual bone has been tabulated but once under its respective heading, whether or not the lesion appeared in the same bone on the opposite side of the body.

[b] Average of years between appearance of primary and bone lesions.

Fifty per cent of the cases of this series were under 15 years of age; 75 per cent, under 20 years of age; and 90 per cent, under 30 years of age.

In the observations made by McCarthy,(17) in 1906, on the prevalence of tertiary lesions in defined localities and among certain classes of people, he gives the frequency of their occurrence and their description as follows:

(1) Chronic thickening of the skin on the palmar surface of the hands and soles of the feet.—The fissures in cases extended only partially through the skin, were painless and dry, and caused no further discomfort than a feeling of uncomfortable roughness over the affected parts.

In others, the cracks extended down to the muscular layer, exuding a sero-purulent discharge and were extremely tender on pressure. The sensibility of the surface of these parts is greatly diminished.

(2) Chronic indolent ulceration of various parts of the body.—These ulcers varied in size from small ones to those of the size of a hand or larger. When not associated with periostitis, the ulcers are painless and heal slowly. When multiple, the general health is greatly impaired, anemia and emaciation set in, and chronic invalidism is caused. Ankylosis caused by cicatricial contraction of extensive ulceration on the flexer aspect of joints has been observed in several cases.

(3) Periostitis and osteitis are other sequelæ frequently seen.—The shaft of the tibia, radius, and ulna are the usual sites of these complications. A swelling resembling a syphilitic node, appears over the shaft of the bones involving all the tissues covering it. This is at first painless. As the growth enlarges, the bones become thickened and the surface of the skin is glazed and purplish, and pain on pressure is present. The skin in time breaks down and troublesome ulceration results. When joints are affected, usually the knee, finger, and elbow-joints, with this variety of the disease, ankylosis results.

Necrosis of the nasal and palate bones resembling the syphilitic affection of this nature, have been seen in several cases.

(4) Cartilaginous tumors on the elbow and knee joints have been observed in nine cases. These tumors were painless, and caused no discomfort except for their size and position. They were ascribed by the sufferers to an antecedent attack of yaws.

Rat,(29) Daniels,(13) and Boissière reported cases with destruction of the nose and palate and discussed the probability of these lesions being due to yaws. Boissière also noted tibial involvement, joint swelling, and dactylitis.

Castellani(9) cites the sequelæ of two cases as follows:

Case 1. Young Singhalese girl of about 14 years of age. No history of syphilis either congenital or contracted: five years of age suffered, together with all other members of the family, from yaws and was treated in a Government Hospital from which she was discharged cured a few months later. She remained in till four months ago when she noticed a slight indolent swelling on the right leg which increased in size and finally broke out leaving a rather large ulceration. Two months later when I examined

her, several ulcers were present in both legs, of irregular shape, thin margins, rather deep and without much secretion; the left tibia was arching forward; moreover on one of the ribs an indolent gumateous-like swelling was present. In the secretions of the ulcers no spirochaetes were found. The girl has been treated with potassium iodide and the ulcers have healed leaving large whitish irregular scars.

Case 2. Singhalese girl about 11 years of age. Sister of the previous patient. No history of syphilis; genital organs intact. Five years ago she suffered from yaws at the same time as her sister. She recovered and remained in good health until three months ago when an ulcerative process developed on the soft palate which at the time I examined her, had already destroyed the uvula. The patient presented the thickening of the metacarpal bones and phalanges which had caused a certain distortion of the right hand. The potassium iodide treatment was begun two months ago, and the patient is rapidly improving, the ulcerative process of the palate being already arrested and healed. No spirochaetes were found in the ulcer.

Ashburn and Craig(1) cite experiments produced by Neisser, Baermann, and Halberstädter(18) where three monkeys (*Macacus cynomolgus*) were inoculated subcutaneously with the bone marrow from a monkey (*Macacus cynomolgus*) infected with frambœsia, with the result that one of the three inoculated with bone marrow developed the disease after an incubation period of forty-four days.

It is very evident that the majority of bone and joint lesions of yaws is the result of a general infection. The explanation of the peculiar selective bone manifestations in some cases may be similar to that of the various manifestations of syphilis due to variations in strains.(18, 21, 22, 23, 31) The experiments attempted by me to reproduce the bone lesions in animals have been so far unsuccessful.

In the treatment of these cases the Castellani(5, 6) mixture was used according to directions, except that a small amount of glycerin was added to improve the taste and so get the patients to take the treatment consistently.

TABLE I.—*Castellani's mixture in the treatment of yaws.*

	Quantity.
Tartar emetic ---------- grains --	1
Sodium salicylate ---------- do ----	10
Potassium iodide ---------- drachm --	1
Sodium bicarbonate ---------- grains --	15
Water q. s ---------- ounce --	1

Salvarsan was used in three of the cases, two of which received 0.4 gram, while the third received 0.2 gram, given intravenously.

In the observation of these cases, over a period of five months,

the effect of the treatment on the regeneration of the bone at the sites of the bone lesions was studied by radiographs taken at monthly intervals as nearly as was practicable. In every case the clinical and subjective symptoms disappeared long before the radiographs showed the bone lesions to have disappeared.

The histories of the most important cases are as follows:

CASE 1

B. U., Filipino, 8 years old. The primary lesion was on the right leg, while the patient was still a nursing baby. The secondary lesions appeared soon afterward and were most manifest on the hands and about the mouth. The secondary lesions gradually disappeared without treatment, but the mother yaw remained for over a year. Five years later the proximal phalanx of the index finger of the right hand became swollen and enlarged. Soon the adjacent fingers became similarly involved, but the patient stated that the fingers were not painful. On February 10, 1917, the X-ray pictures showed a total of nineteen bone lesions including those on the articular surfaces. The Castellani treatment was given in one-half the adult dose, but the patient soon complained of gastric disturbance and headache. The amount was then reduced to one-fourth the adult dose. After five months the bone lesions showed definite improvement, and considerable regeneration of the bones had taken place.

CASE 2

M. S., Filipina, 10 years old. The primary lesion was on the left leg in 1915. The secondary eruption, which appeared six weeks later, gradually disappeared after the third month without treatment. In August, 1916, she complained of pain in the left leg, which condition persisted until she was seen in February, 1917. The X-ray pictures at this time showed one lesion in the lower part of the tibia and four in the os calcis. Further observation of this case was not possible.

CASE 3

P. G., Filipina, 15 years old. The primary lesion appeared on the left leg in October, 1911. This lesion improved without treatment, but did not completely heal. The secondary eruption appeared three weeks later and was most marked upon the feet. Other lesions were scattered about the face, anus, and vulva. After one and one-half years the eruption had disappeared except from the lower extremities. It was elicited that severe rheumatoid pains involving all the joints developed about six months after the appearance of the primary lesion and persisted

during the next four years. During this period of her illness the soft tissues of the middle finger of her left hand became contracted and the finger could not be extended, the external lesions had become large ulcers, and the bone and joints of both extremities were so painful that she suffered constantly. In 1915 she was admitted to a hospital in Manila in a helpless condition. During the two years she remained there the condition was but little relieved, and upon returning to her home she became entirely helpless from the pain she suffered. The ulcerations were deep and painful and emitted a foul odor of decomposition.

When the patient was seen in February, 1917, she weighed 22.68 kilograms (50 pounds) and was 1.1 meters (3.5 feet) in height. There were large areas of scar tissue and of ulceration involving the greater part of the lower extremities. She was badly emaciated and anæmic and cried continuously when she attempted to walk or move about. An X-ray survey of all the bones of her body was made and a total of 52 bone lesions, including those on the articular surfaces, was found. She was given the Castellani treatment in full doses three times a day, one-half hour before meals. She continued to take the treatment regularly for the next two months, but still suffered from the bone and joint pains. The X-ray pictures taken at this time showed very slight improvement of the bone and joint lesions. She was then given 0.4 gram of salvarsan intravenously. The relief of the symptoms was as marvelous as in the cases cited by Strong in his work on cutaneous yaws,(33) in 1910, and the change in the bone and joint lesions became manifest radiographically within a month's time. No more salvarsan was given, but the Castellani treatment was continued until July 1, 1917, when the X-ray pictures showed almost complete regeneration of the bone where the lesions had been. At first the lesions showed a lessened degree of translucency, then a diminution in size, and later a return of the cancellous-tissue appearance.

During the treatment she had persistent thirst, some salivation, and nasal catarrh, but no gastric disturbances.

CASE 4

D. S., Filipino, 7 years old. The primary lesion was on the neck, in June, 1915. One month later the mother yaw began to disappear, and a general secondary eruption followed after a short febrile period. As the secondary eruption disappeared, rheumatoid pains appeared in several of the joints.

When the case was first seen on February 10, 1917, the right

arm was flexed at the elbow and made useless by a contracture on the anterior surface of the joint. This contracture had persisted for the past year. At this time the Castellani treatment was started in one-half the adult dose, and by the end of the second week the contracture had disappeared, but the painful bone lesions persisted for some time. Röntgenograms after full five months' treatment showed a marked improvement of the lesions, but regeneration was not complete. While taking the treatment, the patient vomited on several occasions, showed marked depression on the fifth day, becames salivated, and had severe catarrhal symptoms.

CASE 5

A. G., Filipino, 26 years old. The primary lesion appeared in August, 1914. This lesion persisted about one month. One month later the secondary eruption appeared about the axilla, elbows, mouth, anus, and prepuce, and these lesions disappeared without treatment, but soon afterward contractures of the extremities and severe rheumatoid pains in the feet developed. These conditions existed for about two years, and at the time I first saw him, he was able to get around and do light work. The X-ray pictures showed bone lesions in the left os calcis, on the articular surface of the upper extremity of the left tibia, and on the phalanges of the hands. The patient was started on the Castellani treatment February 10, 1917, and by February 25 marked improvement was evident. To hasten the recovery of the case, 0.2 gram of salvarsan was given intravenously, but the case did not return subsequently and could not be followed.

CASE 6

A. S., Filipino, 60 years old. The primary lesion appeared on the right leg on June 5, 1915. Two months later he developed the secondary eruption and a varicose condition of the veins of the middle finger of the right hand. The finger became twice its normal size and was spindle-shaped, boggy, and worm-like to the touch, but was not painful. (It is questionable if this condition had any relation to the yaws.) He complained of pain in the tibia and femur, which had existed for one year at the time he was first seen on February 10, 1917. The röntgenograms showed a total of ten lesions. Those of the phalanges of the hands showed a marked narrowing of the cortex of the bones, while the one on the upper end of the tibia was on the surface of the bone and was excavated in character. He was given the Castellani treatment, which he took regularly, and

although he stated that his pains had left him, the lesions were still evident by the X-ray after five months' treatment.

CASE 7

C. R., Filipino, 28 years old. The primary lesion was on the right knee in September, 1911. Two months later the secondary eruption appeared, after which there were violent rheumatoid pains in the phalanges on the feet and hands. One year after the initial lesion the distal phalanges were swollen and knoblike. On February 10, 1917, the X-ray showed rarefication of the terminal phalanges of the toes and thinning of the cortex of the phalanges of the hands. He was given the Castellani treatment, but he disliked the medicine, and the case could not be followed.

CASE 8

F. P. (As this case is one from which the description of the bone lesion has been made, a more detailed history will be given as prepared through the kindness of Doctor Domingo, senior house physician at the Philippine General Hospital.) General data: Filipina, 27 years old. Married, housewife by occupation. Born in Parañaque, Rizal, and has lived there ever since. She came to the Philippine General Hospital during the latter part of January, 1917, complaining of pain in the bones and joints, although she also presented several sores on the face, scalp, and neck. Smokes five to seven cigarettes each day.

Family history.—No history of tuberculosis or syphilis. Father and mother living and well. Has seven brothers, one of whom is in the United States, while the rest are in Parañaque. All are living and well, except one, who has the same external lesions as the patient.

Personal history.—The patient had her first menses at the age of 13 and married when 15 years of age. She has had four children, one of whom died of *suba*,[3] one has *bubas*[4] at present, and the other two are well. Has not had any miscarriages. Her husband is living and well and has no history of venereal disease. The youngest child is still nursing the mother.

Previous illness.—None relevant to the present condition.

Present complaint.—Primary lesion started in August, 1916, as a small papule on the anterior aspect of the left ankle. It was neither painful nor itchy. It continued to grow, and about January 16, 1917, when the case was seen with Doctor Guerrero at the Philippine General Hospital, the lesion was about 2 centi-

[3] Infantile beriberi. [4] Yaws.

meters in diameter, in the form of a large round ulcer with more or less irregular edges and elevated granulating surface, from which an abundance of serum could be expressed. Examination of this serum showed twenty or more *Treponema pertenue* to every field. One cubic centimeter of this serum was taken from this lesion for inoculation of animals. In the latter part of October, 1916, the secondary eruption appeared on the face, scalp, neck, abdomen, and vulva. When the patient was admitted to the hospital, these lesions were nearly all circular in outline, although a few of the lesions on the face were more or less elliptical. They were raised from the surface and covered by a thick, hard yellowish crust. Removal of the crust left a raw, granulating surface. Some of the lesions of the face and abdomen were flattened out and deeply pigmented at the edges.

The pains in the bones and joints started in December, 1916, and gradually became more and more intense, until she could hardly walk. The phalangeal joints of the fingers were swollen and painful. No other joints were swollen, but pressure on the bones and other joints produced intense pain. There was no fever nor headache.

Röntgenograms of her hands were at this time taken by Doctors Fernandez and Argüelles, and an abundance of lesions was present in all the bones. The Castellani treatment was given to her by Doctor Guerrero until she left the hospital. I saw the case again on February 25, 1917. The external lesions were healed, but she still complained of pains in the bones. She had continued to take the Castellani treatment rather irregularly. She was induced to take her medicine as prescribed until March 2, when it was learned that she refused to continue with the treatment. Nevertheless she readily submitted to treatment by salvarsan, and 0.4 gram was given intravenously on March 4. The X-ray pictures taken on the same day showed no changes from those taken in February at the hospital. There was a total of 113 lesions. By the end of the second week, after this injection, the patient was entirely relieved of pain. In April the X-ray picture showed a very definite regeneration of the bone at the sites of the lesions. By the early part of July only a few places could be recognized where the lesions had existed.

CASE 9

R. F., Filipino, 16 years old. The primary lesion occurred on the right knee in September, 1911. The secondary eruption appeared one month later and gradually disappeared without treatment. He stated that in 1914 he suffered with pains in

the joints involving the shoulders, elbows, hips, and knees and the phalangeal joints of the fingers and toes. At the time he was seen, February 10, 1917, he was entirely well, except that his right heel was painful. The X-ray pictures showed only one lesion in the os calcis. The case could not be followed.

CASE 22

R. C., Filipino, 15 years old. The primary lesion was on the left knee in 1905. The secondary lesions appeared a few months later and persisted until 1913. No treatment was given. The secondary lesions gradually disappeared, but the mother yaw did not heal. From this time the bones and joints of the lower extremities became painful, and by August, 1916, he was unable to walk. He was in this helpless condition when I saw him on February 25, 1917. The X-ray pictures showed a total of 18 lesions, involving the os calcis, scaphoid, tibia, fibula, and the articular surfaces of the tibia and femur on the right side and the os calcis, tibia, fibula, and the articular surfaces of the bones of the knee joint on the left side. After one month's treatment by the Castellani mixture he was able to walk with considerable ease. The case failed to come for further treatment and could not be followed.

Cases 10, 11, 12, 20, 21, 23, 24, 25, 30, and 31 are of minor interest and are only referred to in Table I.

CONCLUSIONS

1. The majority of cases of yaws with bone and joint involvement shows characteristic X-ray lesions.

2. The radiograph can be used as an additional means of differentiating yaws from syphilis, when there is involvement of the bone, and as a confirmation of the evidence that the two diseases are distinct.

3. The pains complained of in the joints are due, in most part, to the presence of the lesions on the articular surfaces.

4. Twenty per cent of patients infected with yaws develop bone or joint lesions when not treated.

5. Regeneration of the bone is complete at the site of the lesion, if the destruction has not been too great.

6. The Castellani treatment causes a gradual disappearance of the bone and joint lesions.

7. Salvarsan is a specific in these cases, and rapid regeneration of bone follows its use.

I wish to express my appreciation to Doctors Crowell, Guerrero, Fernandez, Domingo, and Argüelles for their help and

courtesies shown while doing this work and to Mr. Hallare, who acted as interpreter and furnished most of the histories of the cases.

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ILLUSTRATIONS

Plate I

Fig. 1. *Case 3.* Multiple yaw lesions in patella and tibia. One variety of painful joints.

2. *Case 2.* Shows three lesions in the os calcis. This involvement is very frequent and makes walking difficult and painful.

Plate II

Fig. 1. *Case 1.* Shows characteristic joint lesion on the articular surface of the bone involved.

2. *Case 3.* Ankylosis following chronic joint lesion of yaws.

Plate III

Fig. 1. *Case 3.* Shows contracture on flexure surface of second finger of right hand. Multiple bone lesions. Large cutaneous lesion and thickening of soft tissues on the palmar surface of index finger of right hand.

2. *Case 3.* Five months later. Shows the disappearance of the contracture. A few of the bone lesions can be distinguished.

Plate IV

Fig. 1. *Case 8.* Mother yaw, before treatment.

2. *Case 8.* Mother yaw, after treatment by the Castellani mixture.

3. *Case 8.* Yaws, secondary eruption, before treatment.

4. *Case 8.* Yaws, secondary eruption, after treatment by the Castellani mixture. This patient also had bone lesions that developed in less than six months after the mother yaw (see Plates V and VI).

Plate V

Fig. 1. *Case 8.* Multiple lesions in the bones that showed no change after six weeks of treatment by the Castellani mixture.

2. *Case 8.* This case showed definite change within one month after the administration of 0.4 gram of salvarsan intravenously. Three months later regeneration of the bone was practically complete.

Plate VI

Fig. 1. *Case 8.* Typical bone lesions of yaws.

2. *Case 8.* Regeneration of the bone at the sites of the lesions.

Plate VII

Fig. 1. *Case 1.* Shows bone and joint lesions before treatment.

2. *Case 1.* Shows lesions five months after treatment by the Castellani mixture. Note lack of regeneration of bone and deformity.

3. Case to show the chronic bone lesions of yaws with deformity. Case of Drs. R. Fernandez and Argüelles.

Fig. 1. Lesions in patella and tibia. Case 3.

Fig. 2. Lesions in os calcis. Case 2.

PLATE I.

Fig. 1. Joint lesions. Case 1.

Fig. 2. Ankylosis, following joint lesion. Case 3.

PLATE II.

Fig. 1. Flexor contracture and multiple bone lesions. Case 3.

Fig. 2. Five months later. Case 3.

PLATE III.

Fig. 1. Mother lesion, before treatment.

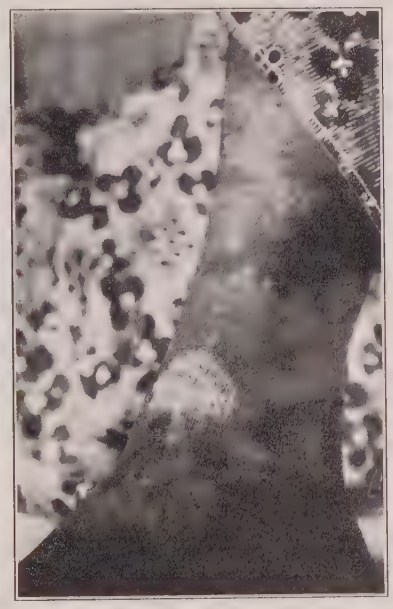

Fig. 2. Mother lesion, after treatment.

Fig. 3. Secondary eruption, before treatment.

Fig. 4. Secondary eruption, after treatment.

PLATE IV. Case 8.

Fig. 1. No bone regeneration after six weeks of Castellani treatment. Case 8.

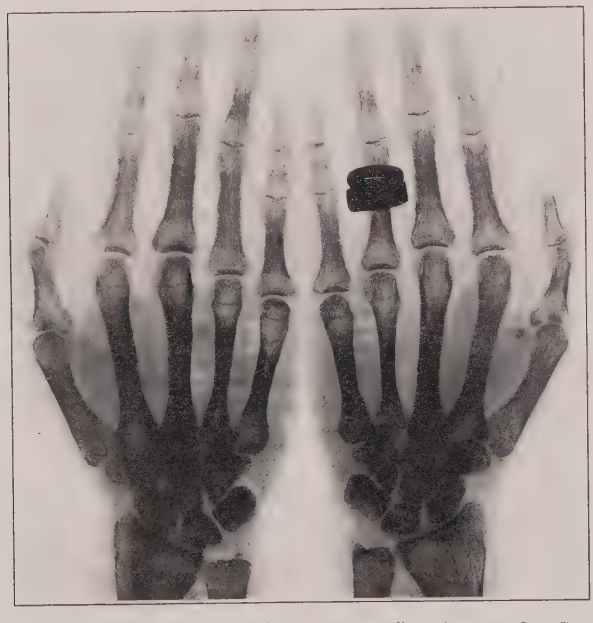

Fig. 2. Regeneration of bone of the same case after salvarsan. Case 8.

PLATE V.

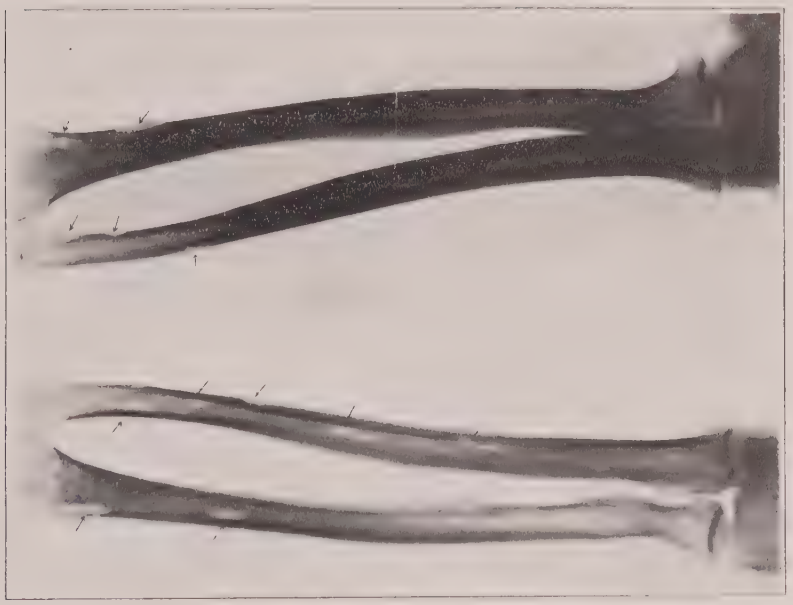

Fig. 1. Typical bone lesions of yaws. Case 8.

Fig. 2. Regeneration of bone at sites of lesions. Case 8. Same as above.

PLATE VI.

Fig. 1. Chronic bone and joint lesions with deformity. Case 1.

Fig. 2. Case 1 five months after treatment by the Castellani mixture.

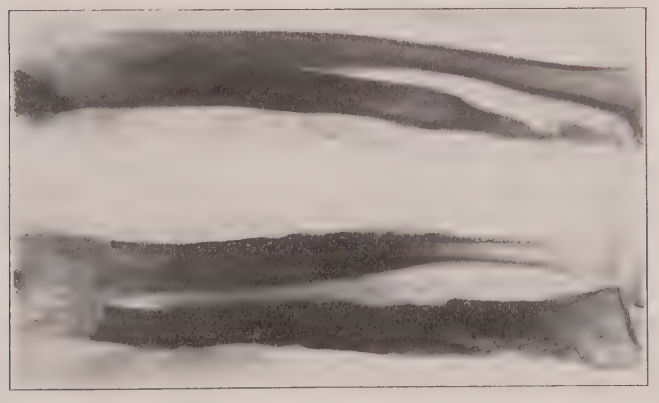

Fig. 3. Chronic bone lesions with deformity. Case from Doctors Fernandez and Arguelles.

PLATE VII.

INFECTIONS WITH COCCIDIUM AND ISOSPORA IN ANIMALS IN THE PHILIPPINE ISLANDS AND THEIR POSSIBLE CLINICAL SIGNIFICANCE [1]

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FIVE TEXT FIGURES

The recent discovery in Manila of several species of Sporozoa, presumably belonging to the order Coccidiida, which have been found infesting animals of common species, brings us face to face with the possibility of human coccidial infections, and the purpose of this paper is to present a few of the facts regarding these infections for the information of physicians who may encounter such conditions in their practice. So far as I have knowledge, no case of human coccidiosis has been reported in the Philippine Islands, but conditions supervening upon the war have led to the discovery in other parts of the world of many cases of undoubted coccidial infection, and these cases, taken in conjunction with older but less exact reports of similar infections, justify us in the belief that coccidiosis of man may in time to come be looked upon as a definite clinical entity and a condition that may crop up at almost any time or place.

In introducing the subject it seems desirable to make it clear just what is meant by coccidia. This term is rather loosely employed to describe a group of Sporozoa that are intracellular parasites, having an asexual cycle within epithelial cells where reproduction takes place by the process known as schizogony, and a succeeding sexual process involving the union of sexually differentiated gametes and spore formation within a cyst. In a general way the life cycles correspond to the classical cycle worked out by Schaudinn in the case of *Coccidium schubergi*. But it must be borne in mind that the terms "coccidium" and "coccidia" are frequently used in a rather loose and general way, and all organisms spoken of as "coccidia" are not necessarily of the genus *Coccidium*. The genus *Coccidium* is only one of a large number of genera grouped under the order Coccidiida. This order is broken up into four families

[1] Read before the Manila Medical Society, November 5, 1917. Received for publication October, 1917.

by Lèger, whose classification I follow: Asporocystidæ, Disporocystidæ, Tetrasporocystidæ, and Polysporocystidæ. The two genera we shall consider in this paper are the genus *Isospora* and the genus *Coccidium,* belonging, respectively, to the families Disporocystidæ, in which the oöcyst contains two sporocysts, and Tetrasporocystidæ, in which the oöcyst contains four sporocysts.

Within the past few weeks the department of medical zoölogy has received material that apparently represents six different kinds of coccidial infection. To Dr. H. Windsor Wade, of the Bureau of Science, we are indebted for calling our attention to an interesting parasite in the kidney of the guinea pig, which may prove to be identical with Seidelin's *Klossiella cobayae,* a member of the family Polysporocystidæ. Dr. Edward S. Ruth, of the department of anatomy, of the College of Medicine and Surgery, has furnished us with material showing a coccidial infection of undetermined nature in the testis of the house lizard. Dr. Elias Domingo, a graduate student in the department of medical zoölogy, has recently found a *Coccidium* and a species of *Isospora* in the intestinal tract of the house lizard. In our own department we have found *Isospora bigemina* in the intestine of kittens, while *Coccidium cuniculi* has been previously reported here in the rabbit. This latter is believed by many authorities to be identical with the parasite that has been reported in man.

This immediately raises the question as to the specificity of these parasites, and at the outset permit me to say that I consider the matter to be far from settled. To be on the safe side, however, it seems to me that we must assume that coccidial infections in animals, of a kind that is apt to be found about our houses, are a source of danger and should be so regarded until the contrary is proved. Let me cite a few examples in support of this contention.

Trypanosoma (*Schizotrypanum*) *cruzi,*(15) the cause of Chagas fever in South America, was first seen in its invertebrate host *Conorhinus megistus,* a blood-sucking hemipterous insect, before it was found in the blood of human beings. Lynch,(13) whose work calls for amplification, has described the rat as a host of *Entamœba histolytica,* the cause of entamœbiasis in man. Lanfranchi(11) has recently become infected with a laboratory strain of either *Trypanosoma brucei* or *Trypanosoma evansi,* both parasites of cattle. Krempf(10) has recently reported a hæmogregarine in man, while the work of Dutton and Todd,(3) Fantham,(4) Fantham and Porter,(6) and others in induced

herpetomoniasis and *Leishmania* infections is strongly suggestive of the possibility of the origin of kala-azar in man from the bites of insects harboring herpetomonads. It is finally beginning to dawn upon us, after many bitter lessons, that in the past we have paid entirely too little attention to the relations between parasites supposed to be specific to lower animals and conditions of disease occurring in man.

In dealing with the problem of coccidiosis in man, we are greatly handicapped by the vagueness and lack of information contained in reports on these infections. We have, so far as I know, no report of clinical or pathological findings in any of these cases, save the case reported by Davaine,(2) which dates back to 1858, which will lend us much help. Until recently the descriptions of the organisms found have been so incomplete as to leave us in doubt, in most cases, as to which genus was involved or, in many other cases, if, indeed, the organism was a protozoön at all. We have no literature on the intracellular phases in the cycle of the human parasite. Some of these reports are of interest to the pathologist, but they leave much to be desired from the viewpoint of the protozoölogist.

Coccidia are typically parasites of epithelial cells during their trophic phases, but Smith (17) has pointed out that they may be found between epithelial cells or even occupying subepithelial positions; however, such conditions are more or less aberrant. Infection takes place through the ingestion of matter contaminated with the spores of the parasites, and liberation of the sporozoites from the sporocysts takes place under the influence of the digestive juices of the small intestine. The sporozoites, which are minute, sickle-shaped bodies, penetrate the cell membrane of the epithelial cells and come to rest in the cytoplasm, on which they proceed to feed. As it feeds, each parasite grows, the host cell becomes enormously hypertrophied, compressing the adjacent cells, and the host-cell nucleus is crowded down to the basement membrane. Finally the trophozoite has reached the limit of size, multiple division (schizogony) takes place, the cell membrane ruptures, and a number of merozoites are set free to infect other epithelial cells. This is the so-called asexual or multiplicative phase in the life cycle, and it is repeated for a variable number of generations until conditions supervene that initiate the sexual or propagative phase, which is spoken of as sporogony.

Sporogony involves the production of sexually differentiated gametes, their union in fertilization, and the subsequent forma-

tion of cysts and spores. The significance of this process is not limited to spore formation, for with fertilization goes a complete rejuvenescence of the organism—a renewal of its vitality, which is not without its clinical significance. The busy practitioner is prone to regard this phase of the life cycle as leading up only to the infection of new hosts, and while this is an important desideratum in regard to future hosts, it yet has a very important bearing on the welfare of the original host.

The belief is very current among protozoölogists that protozoa, like other animals, are endowed with a certain potential of vitality that declines as the organism grows old. That is to say, a protozoön passes through periods that we characterize as youth, maturity, and senescence. With senescence the organism attains a degree of almost total protoplasmic stability, and unless some revitalizing agency intervenes, it dies literally of old age. In nature this rejuvenescence is brought about by the process of fertilization, which seems to be universal throughout the entire animal kingdom, and the organism issues from it endowed with a new potential of vitality with which to cope with the vicissitudes through which it must pass, which, in the case of a parasite, are many.

So it is with the coccidia. The organism passes through many asexual generations, gradually exhausting its vitality. Perhaps, also, there is the added burden of a declining food supply or other unfavorable conditions. In other words, the vitality of the parasite has become lowered, and it must have relief, else it will die.

To this condition the organism reacts by developing its propagative or sexual phase, and once this has been initiated reinfection of the original host becomes impossible except through the original channels—autoinfection ceases. Gradually the schizogonous or asexual cycle ceases, and the intracellular trophozoites become gametocytes, after which stage they are incapable of continuing the infection. The sexual phases develop, the cysts pass out with the fæces, and in time, the host is completely purged of its original infection though not necessarily immune to subsequent infections. Here the necessity for fertilization to restore the flagging vitality of the parasite has been met and has operated to bring about the self-limitation of the disease; spore formation has, in a measure, been incidental.

May this not, in part, explain the lack of information on human coccidial infections? Our information on the symptomatology of human coccidiosis is very meager. Some of the writers speak of diarrhœa, but there they stop. Chronic diarrhœa, unless

accompanied by more urgent symptoms, is frequently treated lightly by the sufferers themselves. It seems from what we know of the self-limitation of many coccidial infections in the lower animals that the same thing may occur in man and pass almost unnoticed, especially in countries where routine examinations of stools are seldom made. Furthermore coccidial cysts are frequently mistaken for the eggs of helminths and vice versa by the inexperienced microscopist.

It may be urged that the very similar life cycle of the malarial parasite and the tendency of old malarial cases to relapse apparently contradict this theory of self-limitation, but I should like to point out that in *Coccidium* and *Isospora* gametogony is completed and sporogony starts and is carried on to an advanced stage in the original host. There is encystment, and the cysts pass out and complete their development before it is possible for them to infect a new or the same host.

In *Plasmodium,* however, we have an alternation of hosts, sporogony being completed within the body of the mosquito. The sexual cycle in man is carried to the gametocyte stage only, and we have no evidence that this stage is infective to the original host. We are left here to speculate as to whether relapses of malarial fever are due to the presence of a relatively small number of trophozoites, which lie dormant in the spleen or bone marrow or which may even be free in erythrocytes in the circulation, or to some autogamous, parthenogenetic, or similar process, as Schaudinn and others have suggested.

It must not be inferred from this that all coccidial infections of this type tend toward spontaneous recovery. In many instances the infections are rapidly fatal. *Cyclospora karyolytica* gives rise to an enteritis in the ground mole, which may bring about a fatal termination in forty-eight hours, the intestinal discharges consisting almost entirely of desquemated epithelium and parasites. Young animals are prone to succumb quickly, and this should make us especially watchful in the case of children, who ordinarily come in closer contact with animals that may harbor parasites than do adults.

The most reliable information regarding coccidial infections in man comes to us from the British workers in the war zone, although Wenyon and O'Connor(23) mention human infections with *Isospora* in Egypt. Fantham (5) reports four cases of coccidial infection, "apparently *Isospora* type," found during the examination of the stools of 1,305 British soldiers in the various hospitals in the western command. These cases were all dysenterics who had become infected chiefly in Gallipoli, al-

though a few were brought in from Flanders. Woodcock (25) had previously reported similar cases that had been received from Gallipoli, which he thought were infections with *Isospora.* The cysts he saw contained one and sometimes two masses of protoplasm. Dr. G. C. Low also came across one case, and Wenyon saw three others at the London Hospital.

Wenyon (21) has reported briefly but intelligibly on these three cases and confirms Woodcock's conjecture that his cases were of *Isospora* infection. Wenyon comments on these cases as follows:

> As the coccidium develops in the intestinal epithelium, it of course brings about destruction of the epithelial cells themselves, and so must be regarded as of some pathogenic importance, although the symptoms of human intestinal coccidiosis have not been definitely determined. In animals, such infections are often the cause of serious enteritis, which may have a fatal termination.

Wenyon continued his study of this parasite (22) and figures the oöcysts in various stages of development. The cysts are oval, measuring 27 μ to 30 μ by 12 μ to 15 μ, and contain two sporocysts, each containing four sporozoites and a mass of residual protoplasm.

In still another paper (20) this same author reports a case of infection with *Coccidium* in a soldier invalided home from Gallipoli. This case is interesting in that the cysts passed by this patient did not in the least resemble the cyst of the rabbit *Coccidium,* but more closely resembled the cysts of *Coccidium falciforme* found in the intestine of the mouse. They were almost spherical, measuring 20 μ in diameter, whereas *Coccidium cuniculi* of the rabbit produces oval cysts that measure 28 μ to 42 μ by 14 μ to 28 μ. The oöcyst of this coccidium, as is to be expected, contains four sporocysts, each containing two sporozoites and a mass of residual protoplasm. In addition to this, the oöcyst of Wenyon's *Coccidium* was not smooth externally like that of *Coccidium cuniculi,* but was covered with irregularities in the form of small nodular ridges and elevations, and the same condition was seen in the sporocysts. Wenyon states that while his *Coccidium* resembles most nearly that of the mouse, it is impossible for him to state definitely if it is actually this species or one quite distinct.

Briefly discussing the matter of the infection of man with both *Isospora* and *Coccidium,* Wenyon says the question is one of great interest. Infection, he says, undoubtedly takes place by way of the mouth, but whether the dust, food, or water, or all three of these are involved remains to be determined. He

adds that the possibility of infection through association with animals that are passing the oöcysts in their fæces must be investigated.

The belief is current that the cysts of coccidia are exceedingly resistant to untoward environmental conditions. Apparently they are much more resistant than the cysts of species of *Entamœba.* It must, however, be said that their impermeability makes it exceedingly difficult to determine whether they are living or not, by the application of the eosin test, which gives such excellent results in the case of *Entamœba.* The department of medical zoölogy is at present conducting a series of tests to determine how long they will retain their vitality under approximately normal and under experimental conditions. This is an investigation that will consume considerable time—several years in fact, but our preliminary investigations show us that they are extraordinarily resistant to a variety of reagents that quickly kill the cysts of *Entamœba.* I have watched, under the microscope, the development of cysts of *Isospora bigemina* in a 3 per cent solution of potassium bichromate, in water treated with thymol, and in double-strength Gram's iodine solution, and I have even seen cysts that would resist the application of Bouin's picro-aceto-formol solution for more than four hours. Other workers have reported on the resistance of coccidial cysts to desiccation, but it is too early to report anything on this from our laboratory.

It would not be surprising to discover that these cysts remain viable after two or even three or more years. Indeed the cysts of *Coccidium avium* have been shown to be infective two years after passage from the intestine of the infected fowl.(7) Mast(14) has shown that the cysts of *Didinium nasutum,* a free-living infusorian, will retain their vitality for a period of five years in air-tight vials. He has found that drying in ordinary atmospheric conditions does not destroy the cysts. In fact, he believes they will live longer dry than in a solution.

However, Wenyon and O'Connor(24) corroborate Kuenen and Swellengrebel in their assertion that the cysts of *Entamœba histolytica* will not withstand drying. They add that cysts of this parasite will survive for thirty days in water, again confirming Kuenen and Swellengrebel. They point out the importance, however, of making a considerable dilution with water to keep down bacterial and fungoid overgrowths that tend to destroy the cysts.

This is in keeping with the findings of Hadley,(9) who advises the study of cyst development in *Coccidium* in 5 per cent

solutions of potassium bichromate, which will arrest putrefactive changes that tend to bring about abnormal development of the cysts.

From the foregoing it will be seen that the disposal of matter containing coccidial cysts may prove to be a very troublesome problem. Quicklime seems to exert the most destructive action on these cysts of any of the disinfectants in common use.

Cysts of species of the genus *Coccidium* are frequently passed in a stage of advanced development, so that they may become infective very soon after they leave the intestinal tract of the original host. But development to the sporozoite stage in the case of *Isospora* does not, as a rule, become complete until two or three days have elapsed after the cysts have left the host. It should be understood that the sporozoites are the end product of sporogony, and they are the form in which the parasite enters the epithelium of the new host. If a cyst in a developmental stage preceding sporozoite formation is taken into the alimentary tract of a new host, the cyst envelope is dissolved and an inert mass of protoplasm is liberated that is incapable of doing harm and that probably very quickly disintegrates.

Notwithstanding the immense amount of work that has been done on this group of the Protozoa, apparently very little has been done on the specificity of these parasites to particular hosts. *Coccidium cuniculi* is generally credited with being infective to rabbits, dogs, cattle, and man, it being suggested that man may become infected through eating livers of rabbits containing the sporocysts of the coccidium. This theory seems to me to be untenable. In the first place the cysts seem to be unable to complete their development in the liver and in many cases eventually degenerate. Furthermore the presence of carbon dioxide in the liver apparently exerts an exceedingly deleterious effect upon them, resulting finally in their destruction. (1) Such a condition is frequently found in old rabbits that have spontaneously recovered from an earlier coccidial infection. But even allowing that these causes may not always be operative, it seems to me hardly likely that the cysts will retain their vitality through the process of cooking, even though they be walled off from the general mass of the liver by connective tissue capsules. A method of infection similar to that obtaining in the case of *Entamœba histolytica* or other protozoa or helminths of similar habitat seems to me much more likely.

On the other hand, on contrasting the two almost similar species, *Coccidium avium* of birds and *Coccidium cuniculi* of the rabbit, it is seen that the rabbit coccidium will not infect birds

and conversely that the bird coccidium will not infect rabbits.

Fig. 1. Cyst of *Isospora cuniculi* in early stage of development.

Isospora bigemina is known to be infective to dogs, cats, and polecats, and is suspected of being infective to man, although Wenyon and O'Connor(23) report negative results on feeding a kitten and a mouse the developed cysts of *Isospora* taken from a human case in Egypt. They add that *Isospora* is frequently found in cats in Alexandria, but that the oöcyst "is quite unlike that of the human parasite. The oöcysts of the cat isospora resemble those of the European form."

However, the size of the oöcysts is not a safe criterion on which to found species any more than is the number of merozoites formed by a schizont in the asexual phase. These variations are found within the species and may be almost as striking as the variations found in the size of the trypanosomes. They are governed largely by conditions within the host—particularly in regard to the food supply. Multiple infections of epithelial cells modify the parasite greatly, and these modifications appear in the asexual phase as reductions in the size of trophozoites and in the number of merozoites produced and in the sexual phase in the production of smaller cysts, this being rather strikingly illustrated by the *Coccidium* found here by Dr. Elias Domingo. In the strain of *Isospora bigemina* carried on in our laboratories the cysts have been uniform in size, no very striking differences having so far appeared.

All of this probably accounts in a large degree for the lack of uniformity in size of the cysts of known species as reported by different observers and points out the need for added information on the problems of cross-infectivity and the dangers these animal species hold for human beings.

Fig. 2. Completely developed cyst of *Coccidium cuniculi*.

Regarding the coccidia on which we are at present working, little can be said at this time, so I shall direct your attention to the illustrations that accompany this article. The cysts of Doctor Domingo's *Coccidium* tend toward the oval in shape, though some are nearly spherical. The oval cysts measure about 20 μ by 16 μ, while those that are spherical measure from 19 μ to 20 μ in diameter, which brings them rather close, in point of size, to the measurements recorded by Wenyon for his human coccidium.

The cysts of *Coccidium cuniculi* range from a

length of 33 μ to 49 μ, with a breadth of from 15 μ to 28 μ. There are few, if any, data regarding the size of *Coccidium cuniculi* cysts recovered from human cases.

Measurements of a few cysts of our cat *Isospora* show a variation in length of from 29 μ to 38 μ and in breadth of from 22 μ to 29 μ, all cysts being oval. These figures do not wholly coincide with measurements of cysts, presumably of the same species, made by other workers. Stiles(18) reports measurements of from 24 μ to 40 μ in length and from 19 μ to 28 μ in breadth, while Swellengrebel(19) gives a length of from 39 μ to 47 μ and a breadth of from 26 μ to 37 μ.

Wenyon apparently had no opportunity to measure large numbers of the cysts of his human *Isospora*, and measurements taken from the scale on his figures give a length of from 27 μ to 30 μ and a breadth of from 12 μ to 15 μ. The coccidium of Railliet and Lucet,(16) which Fantham(8) seems inclined to place in the genus *Isospora*, was reported by these writers to form cysts measuring 15 μ by 10 μ. Lastly Doctor Domingo's *Isospora* of the lizard seems to measure from 16.5 μ to 27.6 μ in length by from 14 μ to 23 μ in breadth.

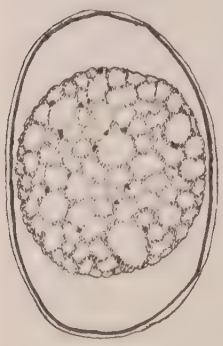

FIG 3. Cyst of *Isospora bigemina* in an early stage of development.

Other figures might be quoted, but it seems to me that they offer us little help in our problem of determining the pathogenicity of the coccidia of the lower animals to man.

And now in conclusion let me say a word about the identification of these cysts. It is probably needless for me to say that this department would welcome the opportunity to work up any material of this nature that may be sent to it. The main thing that the observer must be on his guard against is the confusing of the cysts of helminths, particularly the eggs of trematodes and of hookworms, with coccidial cysts and vice versa. As a rule, the eggs of helminths will be found to be much larger than the sporozoan cysts, but there is no denying the fact that unsegmented eggs of this type do bear a striking resemblance to the oöcysts of coccidia, and this resemblance may even extend to the early stages of segmentation of the eggs, particularly the two-cell stage. The best plan is to dilute the stool with a considerable quantity of water and set a number of the cysts aside in a moist chamber for two or three days.

In the coccidial cysts the protoplasm entirely fills the cyst

in the early stage, but later it contracts to a spherical mass in the center, leaving clear spaces at each pole of the cyst. Eventually this mass divides, in the case of *Isospora* into two masses and in the case of *Coccidium* into four masses. A cyst membrane forms around each of these daughter masses, and some hours later sporozoites and a mass of residual protoplasm can be made out in each of the sporocysts that are contained within the oöcyst. *Isospora* forms four sporozoites in each sporocyst and *Coccidium* two. This establishes the identification beyond a doubt. All these changes may be seen by making examinations of the cysts under the microscope at varying intervals, or the cysts may simply be set aside in the moist chamber for from forty-eight to seventy-two hours and then examined. It is a comparatively simple matter to isolate individual cysts with a capillary pipette under the microscope.

FIG. 4. Cyst of *Isospora bigemina*, showing development of sporocysts.

Finally I desire to say that while I do not predict that coccidia will be found infesting human beings in the Philippine Islands, still, in view of the fact that we have found coccidia in domestic animals here, I see no reason why human coccidiosis should not occur here as it has in other places. It is not hard to see how occasional cases may have been overlooked in the past or may be overlooked in the future. It is on the general practitioner that we must largely rely for the opportunity to develop our knowledge of this very important condition, and the need for that knowledge seems to me to be imperative.

FIG. 5. Completely developed cyst of *Isospora bigemina*.

NOTE.—Since the above was written I have read the paper of Savage and Young,[2] in which they report the finding of six cases of infection with "Coccidium isospora." It seems safe to assume that the writers were dealing with infections by parasites of the genus *Isospora*. Five of these cases were in the hospital under the observation of the authors. All of these five patients were suffering from dysentery. Two had the

[2] Report on the treatment of fifty-nine cases of Entamœba histolytica infection, *Journ. Roy. Army Med. Corps* (1917), 29, 249.

acute entamœbic type, two were bacillary, and one was suffering from a chronic entamœbic infection.

Treatment with emetine compounds had no effect whatever on the sporozoan infection. One case was treated especially for the elimination of the *Isospora,* by the hypodermic administration of emetine hydrochloride over a period of nine days, thirteen grains in all being given. The infection was "practically unaffected." Then silver nitrate injections were tried. A solution of 1 in 2,000, one pint, was given for eight days. The writers report the disappearance of the "coccidia" after three days of treatment; they were found on one occasion only, four days after the last silver nitrate injection. Daily examinations were then made for sixteen days, during which the stools were free from the infection.

However, the authors go on to say that in all the other cases except one the parasites disappeared from the stools without special treatment. This, to say the least, is suggestive of confirmation of the view that the development of sporogony automatically purges the host of its infection in a large proportion of cases. It should not however, give us a false sense of security, for the possibility of liver complications should not be overlooked.

Experience with ipecac and the emetine compounds in protozoan infections other than those with *Entamœba histolytica* should lead us to expect negative results in the treatment of coccidial infections. There is very little evidence to show that either ipecac or emetine has any but the slightest effect on *Entamœba coli* or any of the flagellated protozoa. At the same time it is not certain from the report of Savage and Young that the silver nitrate injections worked a cure in the case in which they were tried. Nevertheless it seems reasonable to assume that in view of the fact that coccidial infections are, for the most part, limited to the epithelial layer of the intestine, local treatment would tend to be more effective than in the case of *Entamœba histolytica,* which works its way deep into the submucosa, where it is safe from the action of drugs similarly applied.

In still another recent article, Castellani [3] states that coccidiosis is comparatively common in the Balkans. He cites fourteen cases reported by Richards from the 43d General Hospital, Salonika, and six cases seen by himself in Macedonia. Of the latter group two, he says, exhibited diarrhœa, but the others

[3] *Journ. Trop. Med. & Hyg.* (1917), **20**, 202.

showed no intestinal symptoms. He describes the treatment as having been unsatisfactory following the use of emetine and a long series of "so-called intestinal disinfectants," all of which yielded very poor results. In two cases methyl blue seemed to act beneficially.

The foregoing data yield us at least thirty-four well-authenticated cases of human coccidiosis of recent occurrence, which should act as a stimulus to future research into this condition.

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ILLUSTRATIONS

TEXT FIGURES

FIG. 1. Cyst of *Coccidium cuniculi* in early stage of development.
2. Completely developed cyst of *Coccidium cuniculi.*
3. Cyst of *Isospora bigemina* in an early stage of development.
4. Cyst of *Isospora bigemina,* showing development of sporocysts.
5. Completely developed cyst of *Isospora bigemina.*

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EXPERIMENTS ON THE TREATMENT OF RINDERPEST WITH VARIOUS DRUGS [1]

By William Hutchins Boynton

(*From the Bureau of Agriculture, Manila*)

The following experiments have been accomplished at various times during a period of approximately six and one-half years. The veterinary division, of the Bureau of Agriculture, is frequently confronted with men who claim to have specific cures for rinderpest, and when their so-called cures are given the proper trial, they are found lacking in curative powers. On account of these frequent claims and rumors of cures it was thought advisable at this time to publish the results of our experiments on various drugs, as these results may aid in obtaining a better idea of a method of treatment and may also give a clearer insight into the location of the fountain head of the virus in the animal body.

In the laboratory only highly susceptible animals are used, which are obtained from localities where rinderpest has supposedly never existed or where a considerable number of years has elapsed since the last appearance of the disease. A highly virulent strain of virus is also used in all the work. The virulence of the strain is kept up by taking the infective material from animals in the early stage of the disease, that is, the first or second day after the initial rise in the temperature. If the infective material is obtained from animals in the last stages of the disease, the virus soon loses its potency, undoubtedly due to the action of the antibodies upon it, which have a tendency to weaken the virus and to render the results unreliable.

If the records of the veterinary division, Bureau of Agriculture, are consulted, it will be notice that in those localities where the cures for rinderpest have been so successful the recovery of animals under normal conditions has been very high, averaging in many instances in the neighborhood of 60 per cent. If the person administering the cure is at all shrewd, he can easily eliminate the doubtful cases and in that way obtain a high percentage of recoveries from his drugs, providing the drugs are not too harmful to the animals and are administered in small enough doses.

[1] Published in *Phil. Agr. Rev.* (1917), 10, 272.

The drugs used in the following experiments were as follows: (1) Eosin; (2) medicinal methylene blue (Merck); (3) cacodylate of soda; (4) atoxyl; (5) quinine sulphate; (6) camphorated oil; (7) creolin; (8) permanganate of potash; (9) ergot; (10) iodine; (11) potassium iodide; (12) gentian violet; (13) adrenalin hydrochloride; (14) nuclein; (15) formalin; (16) chlorazene; (17) castor oil; (18) alcohol; (19) fluid extract of nux vomica; and (20) fluid extract of gentian.

With the small amount of experimentation that has been given to each drug, no promising results have been obtained by the method in which they were administered and the dosage in which they were given.

In all the experiments where sodium chloride solution was made use of to dilute the drug for intravenous and intraperitoneal injections, 0.85 per cent was used. It was found when giving large intravenous and intraperitoneal injections that if the fluid was warmed to about 41° C. the animals withstood the injections with much less discomfort than when the solutions were cooler. All the large intravenous injections were performed in the manner illustrated in Plate I.

EOSIN

Eosin was used with the idea that it might have a special affinity for the virus of rinderpest, at it is one of the diffuse stains and penetrates well.

EXPERIMENT 1

Batanes bull 3153, which had contracted rinderpest by exposure to sick animals and had run a high temperature for forty-eight hours, was injected subcutaneously on the afternoon of May 30, 1911, with 2 grams of Grubler's W. Gelb eosin dissolved in 100 cubic centimeters of sterile distilled water.

July 1 this animal's temperature subsided to normal, but it developed inappetence and diarrhœa and died July 3, presenting good lesions of rinderpest upon autopsy. The subcutaneous and mesentery tissues had taken on a pinkish coloration, resulting from the free distribution of eosin throughout the body, which apparently had no ill effects upon the virus of rinderpest.

MEDICINAL METHYLENE BLUE

Methylene blue was used in experiments 2 and 47 with the idea that if perchance the virus of rinderpest was an intracorpuscular organism this dye might have a direct action upon it, as is the case in malaria. Its antipyretic and anodyne actions were also considered.

EXPERIMENT 2

Batanes bull 3116 was injected on May 23, 1911, with 30 cubic centimeters of filtered blood handled as follows: Five cubic centimeters of virulent rinderpest blood from bull 3135 was diluted up to 500 cubic centimeters with sterile 0.85 per cent sodium chloride solution; this diluted blood was then passed through a Berkefeld N. filter under 3 kilograms' pressure.

This animal presented its first rise in temperature on the morning of May 28, registering 39.2° C.

During the afternoon of May 29, or thirty-six hours after the first rise in temperature, this animal was injected subcutaneously with 2 grams of Merck's medicinal methylene blue dissolved in 100 cubic centimeters of sterile distilled water.

May 30 this animal's urine was dark blue. Its visible mucous membranes also took on a bluish coloration.

May 31, diarrhœa, eating little.

June 1–3, diarrhœa, not eating.

June 4, died, presenting good lesions of rinderpest upon autopsy.

The methylene blue thus administered had no apparent ill effect upon the virus of rinderpest.

CACODYLATE OF SODA

Cacodelate of soda was tried with the idea that it might have an action upon the virus of rinderpest similar to that which it has upon *Treponema pallidum*, although arsenobenzol (salvarsan, 606) has been tried on rinderpest with negative results. (The reference to the experiments with salvarsan cannot be located.)

EXPERIMENT 3

Carabao 3088 had contracted rinderpest by exposure to sick animals.

May 17, 1911, the fourth day of temperature, this animal was injected intravenously in the femoral vein with 6 grains of cacodylate of soda. The animal's temperature subsided to normal in one and one-half days after the injection, but it suffered severely from photophobia; diarrhœa, not eating.

The animal died the night of May 19, presenting marked lesions of rinderpest.

EXPERIMENT 4

Batanes bull 3158.—This animal had been injected with virulent rinderpest blood.

May 19, 1911, which was the second day of temperature, this animal was injected intravenously in the femoral vein with 5.25

grains of cacodylate of soda. The temperature decreased on May 20, but the animal presented marked symptoms of photophobia.

May 21–23, diarrhœa, not eating.

This animal died May 23, presenting marked lesions of rinderpest upon autopsy.

EXPERIMENT 5

Batanes bull 3135.—This animal had been injected with virulent rinderpest blood.

May 23, 1911, eighteen hours after the first rise in temperature, this animal was injected intravenously in the femoral vein with 3 grains of cacodylate of soda.

May 24, this animal presented symptoms of photophobia.

May 25, eating little.

May 26–28, diarrhœa, not eating.

May 28, died of rinderpest, presenting marked lesions.

From the results of experiments 3, 4, and 5, it will be seen that cacodylate of soda as it was used in these cases had no ill effect upon the virus of rinderpest and, if anything, aggravated the disease, causing a much more pronounced photophobia than is normally present in rinderpest and also more pronounced intestinal lesions than are usually noticed. From these results it appears that arsenic compounds are contraindicated in rinderpest.

ATOXYL

Atoxyl was tried because it has such a pronounced action in clearing the blood stream of trypanosomes in cases of surra infection, and there was a possibility that it might have a similar action upon the virus of rinderpest.

EXPERIMENT 6

Batanes bull 3119.—This animal had been injected with 30 cubic centimeters of virulent rinderpest blood serum [2] on July 8, 1911.

July 11, it presented a rise in temperature, registering, in the afternoon, 40.2° C.

July 12, it developed a diarrhœa.

July 14, which was the third day after the initial rise in temperature, this animal was injected subcutaneously with 5 grams of atoxyl dissolved in 60 cubic centimeters of sterile distilled water.

[2] Virulent rinderpest blood was allowed to stand in the ice box for twenty-four hours, then the serum was drawn off and injected.

The animal's temperature dropped to slightly high normal shortly after the injection, registering 39.4° C., but it presented marked symptoms of photophobia.

July 16, this animal died, presenting marked lesions of rinderpest upon autopsy.

The atoxyl gave symptoms similar to those of the cacodylate of soda and appeared to stimulate the virus instead of retarding its action.

QUININE SULPHATE

Quinine sulphate was used with the idea that it might have an action upon the virus of rinderpest similar to that which it has upon malaria. Its antipyretic action was also taken into consideration.

EXPERIMENT 7

Batanes bull 4315.—This animal was injected on November 24, 1911, with 25 cubic centimeters of rinderpest blood that had been kept in a clotted form in a large test tube for ninety-six hours in the incubator at 37° C. The clotted blood was taken from the test tube and macerated in a sterile mortar with a 5 per cent potassium citrate solution, and the liquid material thus obtained was injected.

November 30, in the forenoon, this animal presented its first rise in temperature, registering 39.6° C.

December 1–2, diarrhœa, eating little.

December 3–4, diarrhœa, not eating.

December 4, this animal was given quinine sulphate in capsules per orum in the following doses:

	Grams.
8.30 a. m.	5
11.30 a. m.	5
2.30 p. m.	5
5.30 p. m.	5

This animal died during the night of December 4 and presented good lesions of rinderpest upon autopsy.

From this experiment it will be noted that the animal received 20 grams of quinine sulphate per os with no effect upon the disease, although it was in the last stages of the disease when the treatment was undertaken.

EXPERIMENT 8. QUININE SULPHATE AND ERGOT

Fuga carabao 67.—This animal was injected on January 28, 1917, with 50 cubic centimeters of virulent rinderpest blood from carabao 65.

January 29 this animal received intraperitoneally 8 grams of quinine sulphate dissolved in 1,000 cubic centimeters of sterile distilled water slightly acidulated with sulphuric acid. The injection was made at this time to try to abort the disease. In two hours after this injection the carabao was lying down, eating little, and presenting slight nervous symptoms.

January 30, this animal was standing up and eating well, but had a forenoon temperature of 38.9° C. and an afternoon temperature of 39.5° C.

January 31, afternoon temperature 40.5° C. The animal looked bright and was eating well.

February 1, forenoon temperature 39.9° C.; administered intraperitoneally 10 grams of quinine sulphate dissolved in 1,000 cubic centimeters of acidulated 0.85 per cent sodium chloride solution; afternoon temperature 40° C.; not eating; carabao standing up.

February 2, forenoon temperature 39° C.; diarrhœa starting; slight discharge from eyes; administered subcutaneously 8 cubic centimeters of fluid extract of ergot; afternoon temperature 39.8° C.; diarrhœa, not eating.

February 3, forenoon temperature 39.7° C.; animal very sick; sunken eyes; arched back; drooling; grinding teeth; swallowing frequently; diarrhœa, not eating; blood-stained slugs of mucus in fæces; administered 10 cubic centimeters of fluid extract of ergot subcutaneously.

February 4, carabao 67 found dead in the morning; autopsy presented good lesions of rinderpest.

EXPERIMENT 9. QUININE SULPHATE AND IODINE

Batanes cow 4168.—This animal was injected January 19, 1917, with 50 cubic centimeters of virulent rinderpest blood from bull 4164.

January 22, this animal presented its first rise in temperature, registering, in the forenoon, 39.7° C.; administered intraperitoneally 2 grams of quinine sulphate dissolved in 500 cubic centimeters of acidulated sodium chloride solution and intravenously with 1,000 cubic centimeters of sodium chloride solution in which 0.75 gram of iodine and 2 grams of potassium iodide had been dissolved; afternoon temperature 39.7° C.; muzzle moist; urine dark.

January 23, forenoon temperature 40° C.; animal looked bright; eating; fæces slightly coated with mucus containing a few flakes of blood; administered intraperitoneally 3 grams of quinine sulphate dissolved in 500 cubic centimeters of acidulated 0.85 per cent sodium chloride solution; afternoon temperature

40.5° C.; animal active; muzzle moist; nostrils looked normal; eating little.

January 24, forenoon temperature 39.5° C.; no diarrhœa; looked bright; eating little; administered intraperitoneally 3 grams of quinine sulphate dissolved in 500 cubic centimeters of acidulated sodium chloride solution.

Afternoon temperature 40° C.; not eating.

January 25, forenoon temperature 39° C.; slight diarrhœa; not eating; swallowing frequently; grinding teeth; looked fairly bright; administered intraperitoneally 3 grams of quinine sulphate dissolved in 500 cubic centimeters of acidulated sodium chloride solution.

Afternoon temperature 39.6° C.; diarrhœa, not eating.

January 26, cow 4168 found dead in the morning; autopsy presented marked lesions of rinderpest; intestinal hemorrhage very pronounced.

EXPERIMENT 10. QUININE SULPHATE, IODINE, AND ERGOT

Batanes cow 4172.—This animal was injected January 22, 1917, with 50 cubic centimeters of virulent rinderpest blood from No. 4186.

January 25, this animal presented its first rise in temperature, registering in the afternoon 40.3° C.

January 26, forenoon temperature 39.3° C.; diarrhœa, not eating; administered intraperitoneally 5 grams of quinine sulphate dissolved in 500 cubic centimeters of acidulated sodium chloride solution. It was also injected intravenously with 1,000 cubic centimeters of sodium chloride in which had been dissolved 1.5 grams of iodine and 4 grams of potassium iodide. The animal withstood the injection well. The afternoon temperature was 38.4° C., which was the average normal temperature for the healthy animals this day.

January 27, forenoon temperature 38.2° C.; diarrhœa, not eating; animal did not possess good coördination of movement; muzzle moist; administered subcutaneously 8 cubic centimeters of fluid extract of ergot; afternoon temperature 38.8° C.

January 28, forenoon temperature 37.7° C.; diarrhœa, not eating; animal lying down; respiration catchy; blood in fæces; large amount of mucus; administered subcutaneously 5 cubic centimeters of fluid extract of ergot.

Afternoon temperature 38.8° C.; diarrhœa; better in appearance; breathing regular; lying down; not eating, but drinking a little.

January 29, animal found dead in the morning. Upon autopsy

the fauces presented good lesions of rinderpest. The intestinal tract did not show marked hemorrhagic lesions.

IODINE

Iodine was experimented with after reviewing the results of the work done by Lambert,(1) in which he proves that iodine can be used in strong enough dilution to destroy staphilococci and still have no deleterious action upon living tissue cells. It was thought that by using iodine in sufficiently large doses there might be a possibility of destroying or attenuating the virus to such an extent that the animal would be able to develop resistance enough to recover. Potassium iodide was used to facilitate the solution of iodine and also to have a direct action upon the lymphatic system, which is markedly affected in rinderpest.

EXPERIMENT 11. IODINE AND POTASSIUM IODIDE

Batanes bull 4164.—This animal was injected January 13, 1917, with 50 cubic centimeters of virulent rinderpest blood from No. 4165.

January 16, this animal presented a rise in temperature, registering, in the afternoon, 40° C.

January 17, forenoon temperature 39.7° C.; afternoon, 40.2° C.; diarrhœa.

January 18, forenoon temperature 39.5° C.; diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which were dissolved 0.5 gram of iodine and 1 gram of potassium iodide; withstood injection well; afternoon temperature 39.8° C.

January 19, forenoon temperature 37.4° C.; diarrhœa, not eating; animal very sick; lying down; thick mucus discharge from nose; eyes sunken; grinding teeth; swallowing frequently; blood and mucus in fæces; catchy respiration.

This animal died during the morning of the 19th. Upon autopsy it presented marked intestinal lesions of rinderpest.

CREOLIN

Creolin was used with the idea of trying to disinfect the blood, by either killing or attenuating the virus of rinderpest to such an extent that the animal would be able to acquire enough resistance to combat the disease.

EXPERIMENT 12

Davao carabao 3271.—This animal was injected November 14, 1911, with 50 cubic centimeters of virulent rinderpest blood from No. 3225.

November 21, this animal presented its first rise in temperature, registering, in the afternoon, 39.9° C.

November 25–26, diarrhœa, not eating; congested eye; erosions in mouth; rash under tail.

November 27, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of 1.5 per cent creolin solution in 0.85 per cent sodium chloride; animal withstood the injection well.

November 28–29, diarrhœa, not eating; animal very sick.

November 30, animal found dead in the morning; typical lesions of rinderpest upon autopsy.

EXPERIMENT 13

Batanes bull 3306.—This animal was injected on November 21, 1911, with 25 cubic centimeters of virulent rinderpest blood that had been kept in a test tube at 37° C. for twenty-four hours.

November 26, this animal presented a forenoon temperature of 39.2° C.; afternoon, 41° C.

November 27, administered intravenously 1,000 cubic centimeters of a 1.5 per cent creolin solution in 0.85 per cent sodium chloride; the animal withstood the injection well.

November 29, not eating.

November 30, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of a 3 per cent creolin solution in 0.85 per cent sodium chloride; the animal withstood the injection well.

December 1–5, diarrhœa, not eating.

December 6, died during the morning, presenting typical lesions of rinderpest.

EXPERIMENT 14

Davao carabao 3183.—This animal was injected on November 29, 1911, with 50 cubic centimeters of virulent rinderpest blood from No. 3307.

December 3, this animal presented its first rise in temperature, registering, in the afternoon, 40.2° C.

December 5, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of a 3 per cent creolin solution in distilled water; also given a weak creolin solution to drink.

December 6, not eating; blood in urine.

December 7, diarrhœa, not eating.

December 8, died during the morning, presenting good lesions of rinderpest.

EXPERIMENT 15

This experiment was made to test the infectivity of blood of an animal that had been given a 3 per cent creolin solution intravenously.

Batanes bull 3314.—December 6, 1911, this animal was injected with 25 cubic centimeters of blood taken from carabao 3183, twenty-four hours after this carabao had been injected intravenously with 1,000 cubic centimeters of a 3 per cent creolin solution. This injection was made to ascertain whether or not the virus had been killed in the blood by this heavy injection of creolin.

December 9, this animal presented a rise in temperature, registering, in the forenoon, 39.2° C.; in the afternoon, 40.1° C.

December 11–12, eating little.

December 13–14, diarrhœa, eating little.

December 15–21, diarrhœa, not eating.

December 22–23, bloody diarrhœa, not eating.

December 24, this animal died, presenting good lesions of rinderpest upon autopsy.

This proves that the virus was in virulent form in the blood of carabao 3183 at the time it was drawn and that the creolin had apparently no detrimental effect upon the virus.

PERMANGANATE OF POTASH

Like creolin, permanganate of potash was tried for its antiseptic effect upon, and its possible attenuation of, the virus. Walker(3) has used permanganate of potash on animals sick with rinderpest and has obtained some favorable results. However, he was working with animals having a high natural immunity to the disease, which undoubtedly accounts for much of his success.

EXPERIMENT 16

Batanes bull 3307.—This animal was injected on November 22, 1911, with virulent rinderpest blood that had been kept in a test tube in a clotted form for forty-eight hours at 37° C.

November 27, this animal presented its first rise in temperature, registering, in the forenoon, 39.7° C.; in the afternoon, 40.6° C.

November 29, diarrhœa beginning.

November 30, diarrhœa, not eating; administered subcutaneously 900 cubic centimeters of a 1–2,000 solution of permanganate of potash in physiological salt solution.

December 1–2, diarrhœa, not eating.

December 3, this animal was found dead in the morning and presented good lesions of rinderpest upon autopsy.

EXPERIMENT 17

Batanes bull 3309.—This animal was injected on November 23, 1911, with 25 cubic centimeters of virulent rinderpest blood that had been kept in a test tube in a clotted form for seventy-two hours at 37.° C.

November 29, bull 3309 presented its first rise in temperature, registering, in the afternoon, 40.2° C.

December 1, eating little; administered intravenously 1,000 cubic centimeters of a 1–1,000 solution of potassium permanganate in physiological salt solution.

December 2, eating little.

December 3–4, diarrhœa, eating little.

December 5, diarrhœa, not eating.

December 6, died, presenting good lesions of rinderpest.

EXPERIMENT 18

Batanes bull 3315.—This animal was injected on November 24, 1911, with 25 cubic centimeters of virulent rinderpest blood that had been kept in a test tube in a clotted form for ninety-six hours at 37° C.

November 30, bull 3315 presented its first rise in temperature, registering, in the forenoon, 39.6° C.; in the afternoon, 40.8° C.

December 1, diarrhœa, eating little.

December 2, diarrhœa, eating little; administered intravenously 1,000 cubic centimeters of a 1–500 solution of potassium permanganate in physiological salt solution.

December 3, diarrhœa, not eating.

December 4, diarrhœa, not eating; died during the afternoon, presenting good lesions of rinderpest.

EXPERIMENT 19

Davao carabao 3184.—This animal was injected on November 29, 1911, with 50 cubic centimeters of virulent rinderpest blood from No. 3307.

December 4, carabao 3184 presented its first rise in temperature, registering, in the afternoon, 40.1° C.

December 5, a 1–300 solution of potassium permanganate was being administered intravenously, but the animal died during the injection.

From the four preceding experiments it will be noticed that potassium permanganate, whether administered subcutaneously

or intravenously, had apparently no detrimental effect upon the virus of rinderpest.

FORMALIN

Formalin was used on account of its potent antiseptic value, with the idea of destroying or attenuating the virus of rinderpest to such an extent that the animal would be able to recover.

EXPERIMENT 20

Dalupiri carabao 3182.—This animal was injected on November 29, 1911, with 50 cubic centimeters of virulent rinderpest blood from No. 3307.

December 3, this animal presented its first rise in temperature, registering, in the afternoon, 40.9° C.

December 4, administered intravenously 1,000 cubic centimeters of a 1–4,000 formalin solution in physiological salt solution.

December 6–7, not eating.

December 8, diarrhœa, not eating.

December 9, diarrhœa, eating little.

December 12, temperature normal; eating; no diarrhœa. This animal made a good recovery.

EXPERIMENT 21

Chinese bull 743 contracted rinderpest by exposure during shipment between Hongkong and Manila. This animal was in the last stages of rinderpest when treatment was tried. Bloody diarrhœa, not eating; catchy respiration; marked discharge from nostrils; still able to stand up.

July 14, 1917, administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 5 cubic centimeters of 40 per cent formalin had been added. This animal died during the injection, about 600 cubic centimeters having been administered when death occurred.

EXPERIMENT 22

Chinese bull 742 contracted rinderpest by exposure during shipment between Hongkong and Manila. This animal was very sick; bloody diarrhœa; not eating, but strong.

July 14, 1917, administered intravenously 1,000 cubic centimeters of 0.85 per cent sodium chloride solution to which 1.5 cubic centimeters of 40 per cent formalin had been added; animal withstood injection well.

July 15, diarrhœa, not eating; flakes of blood in fæces; looked bright.

July 16, administered intravenously 1,000 cubic centimeters of sodium chloride solution to which were added 2.5 cubic centimeters of 40 per cent formalin; withstood injection well.

July 17–20, looked very sick; diarrhœa, not eating.

July 21, died this forenoon; typical rinderpest lesions.

EXPERIMENT 23

Fuga carabao 137 contracted rinderpest by exposure to infected animals.

July 14, 1917, this animal presented its first rise in temperature, registering, in the afternoon, 39.9° C.

July 15, forenoon temperature 39.6° C.; afternoon, 40.4° C.; administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 2 cubic centimeters of 40 per cent formalin had been added; withstood injection well.

July 16, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 2.5 cubic centimeters of 40 per cent formalin had been added; withstood injection well.

July 17–20, diarrhœa, not eating; very sick; arched back; discharge from nostrils and eyes; blood in fæces.

July 20, died, presenting good lesions of rinderpest.

EXPERIMENT 24

Jolo carabao 108.—Contracted rinderpest by exposure to sick animals.

July 14, 1917, this animal presented its first rise in temperature, registering, in the forenoon, 39.1° C.; in the afternoon, 40.2° C.

July 15, administered intravenously 1,000 cubic centimeters of sodium chloride solution to which had been added 2 cubic centimeters of 40 per cent formalin; withstood injection well.

July 16, diarrhœa, eating little; administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 2.5 cubic centimeters of 40 per cent formalin had been added; withstood injection well.

July 17–19, diarrhœa, not eating; very sick.

July 19, died, presenting good lesions of rinderpest.

EXPERIMENT 25

Fuga carabao 131.—Contracted rinderpest by exposure to sick animals.

July 14, 1917, this animal presented its first rise in temperature, registering, in the afternoon, 39.6° C.

July 16, administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 2.5 cubic centimeters of 40 per cent formalin had been added.

July 17–20, diarrhœa, not eating; very sick; blood in fæces; mucopurulent discharge from nostrils and eyes.

July 20, died, presenting good lesions of rinderpest.

EXPERIMENT 26

Fuga carabao 132.—Contracted rinderpest by exposure to sick animals.

July 14, 1917, this animal presented its first rise in temperature, registering, in the afternoon, 40° C.

July 15, diarrhœa, not eating.

July 16, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution to which 2.5 cubic centimeters of 40 cent formalin had been added; withstood injection well.

July 17–18, diarrhœa, not eating; very sick.

July 18, died presenting good lesions of rinderpest.

In the seven experiments just described, it will be noted that one animal, Dalupiri carabao 3182, experiment 20, recovered from rinderpest. From the results of the six other experiments it may be granted that the administration of formalin played no part in the recovery, as this animal would undoubtedly have recovered without any treatment, as many animals do.

GENTIAN VIOLET

Gentian violet was used in this experiment with the idea that it might have some direct action upon the virus. Russell(2) has found in his research work that gentian violet has a direct action upon protozoa in high dilution, but has no detrimental effect upon tissue growing in vitro.

EXPERIMENT 27

Batanes bull 3931 was inoculated with rinderpest culture on July 12, 1915.

July 16, this animal presented its first rise in temperature.

July 19, administered intravenously 1,000 cubic centimeters of sodium chloride solution that had 2 grams of gentian violet dissolved in it; took injection well.

July 21–22, not eating.

July 22, died, presenting good lesions of rinderpest, showing that the virus was not affected by the injection.

SERUM, NUCLEIN, AND ADRENALIN CHLORIDE

Nuclein was used to try to develop a leukocytosis in the animals and thus increase their resistance, since one of the chief symptoms in rinderpest is a leukopenia.

Adrenalin chloride was used to tone up the blood-vessel walls, since in rinderpest the virus or its product has a direct action upon the capillary walls, causing them to lose their tone and thus become markedly distended with blood, which leads to stasis, diapedesis, and exudation, the exudates coagulating and causing coagulation necrosis.

The serum was injected to give the animal a supply of antibodies and thus increase the resistance.

EXPERIMENT 28

Batanes bull 4165.—This animal was inoculated on January 5, 1917, with 50 cubic centimeters of virulent rinderpest blood from bull 4162.

January 9, bull 4165 presented its first rise in temperature, registering, in the forenoon, 39.2° C.

January 10, in the forenoon, administered subcutaneously 200 cubic centimeters of antirinderpest serum and 15 cubic centimeters of nuclein solution; in the afternoon, 10 cubic centimeters of adrenalin chloride.

January 11, in the forenoon, administered subcutaneously 15 cubic centimeters of nuclein solution and 10 cubic centimeters of adrenalin chloride; in the afternoon, administered 15 cubic centimeters of nuclein solution and 10 cubic centimeters of adrenalin chloride.

January 12, in the forenoon, animal looked bright; slight diarrhœa; temperature 38.5° C.; administered subcutaneously 15 cubic centimeters of nuclein solution and 10 cubic centimeters of adrenalin chloride; in the afternoon, not looking so well; diarrhœa, not eating; administered 15 cubic centimeters of nuclein solution and 10 cubic centimeters of adrenalin chloride; temperature 38.8° C.

January 13, animal very weak; temperature 36° C.; administered 10 cubic centimeters of tincture of nux vomica and 10 cubic centimeters of 70 per cent alcohol.

Animal died in the afternoon, presenting good lesions of rinderpest.

Although the administration of nuclein and adrenalin chloride appeared to hold in check the more severe symptoms of rinderpest for some time, it has no effect upon the final termination of the disease.

DAKIN'S CHLORAZENE

Dakin's chlorazene was used with the idea of either destroying or attenuating the virus of rinderpest to such an extent that the animal would be able to overcome the disease and recover.

Chlorazene is an ideal antiseptic to use, since it has no corrosive action. It neither precipitates nor coagulates proteins, such as blood serum. It is practically nontoxic even when injected hypodermically. It is extremely stable and is a powerful disinfectant in very high dilutions.

EXPERIMENT 29

Batanes bull 4322.—This animal contracted rinderpest by exposure to sick animals.

July 15, 1917, bull 4322 presented its first rise in temperature, registering, in the forenoon, 38.9° C.

July 17, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 13.8 grains of chlorazene had been dissolved; animal took injection without a struggle.

July 18, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved; the animal began to eat immediately after injection.

July 20, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved; withstood injection well.

This animal did not develop any symptoms of rinderpest except a rather high normal temperature, and it was thought possible that a cure had been effected. It was left in immediate contact with animals in various stages of the disease.

July 29, bull 4322 again presented a high temperature, registering, in the forenoon, 39° C.; in the afternoon, 40° C.

August 1, as this animal continued to run a high temperature, it was decided to administer chlorazene again. It received intravenously 1,000 cubic centimeters of sodium chloride solution in which 4 grams of chlorazene had been dissolved.

August 3, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 4 grams of chlorazene had been dissolved.

August 4, diarrhœa, not eating; very sick.

August 5, died during the night of August 4, presenting good lesions of rinderpest.

There is a question as to whether bull 4322 was suffering from rinderpest during the first administration of the drug. If it was suffering from rinderpest, the chlorazene injections evi-

dently destroyed the virus and also the few antibodies that may have been formed, as the second attack was as virulent as is noticed in any untreated animal, and the administration of chlorazene during this attack had no ill effect upon the virus.

EXPERIMENT 30

Fuga bull 4305.—This animal contracted rinderpest by being inoculated with material from bull 4298.

July 17, 1917, afternoon temperature 40.3° C.

July 18, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 2 grams of chlorazene had been dissolved; animal withstood injection well.

July 19, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved.

July 20, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved.

July 21–22, not eating.

July 23, bloody diarrhœa; not eating; administered 2,000 cubic centimeters of sodium chloride solution in which 10 grams of chlorazene had been dissolved.

July 24, found dead in the morning; good lesions of rinderpest.

EXPERIMENT 31

Jolo carabao 96.—This animal contracted rinderpest by exposure to sick animals.

July 18, 1917, carabao 96 presented its first rise in temperature, registering, in the forenoon, 39° C.; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 3 grams of chlorazene had been dissolved.

July 19, diarrhœa; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved.

July 20, diarrhœa, not eating; administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 10 grams of chlorazene had been dissolved.

July 21, diarrhœa, not eating, sunken eyes; discharge from nostrils; arched back; lopping ears; ulcers in mouth.

July 22, diarrhœa, not eating; administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 10 grams of chlorazene had been dissolved.

July 23, found dead in the morning; good lesions of rinderpest.

EXPERIMENT 32

Fuga carabao 129.—This animal contracted rinderpest by exposure to sick animals.

July 18, 1917, carabao 129 presented its first rise in temperature, registering, in the afternoon, 39° C.

July 19, administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 6 grams of chlorazene had been dissolved.

July 20, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved.

July 21, diarrhœa, not eating; administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 12 grams of chlorazene had been dissolved.

July 22, diarrhœa, not eating; very sick.

July 23, bloody diarrhœa; not eating; sunken eyes; discharge from nostrils and eyes; ulcers in mouth; swallowing frequently; catchy respiration.

July 24, animal found dead in the morning; marked lesions of rinderpest.

EXPERIMENT 33

Batanes bull 4314.—This animal contracted rinderpest by exposure to sick animals.

July 20, 1917, bull 4314 presented a forenoon temperature of 40.2° C.; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 6 grams of chlorazene had been dissolved.

July 21, administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 12 grams of chlorazene had been dissolved; withstood injection well.

July 22, bloody diarrhœa; not eating.

July 23, bloody diarrhœa; not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved; also intraperitoneally 1,000 cubic centimeters of sodium chloride solution in which 5 grams of chlorazene had been dissolved.

July 24, bloody diarrhœa; not eating.

July 25, diarrhœa, not eating; flakes of blood in mucus.

July 26, diarrhœa, not eating; flakes of blood in mucus; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 4 grams of chlorazene had been dissolved.

July 27, found dead in the morning; typical lesions of rinderpest.

EXPERIMENT 34

Fuga bull 4311.—This animal contracted rinderpest by exposure to sick animals.

July 20, 1917, bull 4311 presented its first rise in temperature, registering, in the forenoon, 38.8° C.

July 21, diarrhœa, not eating; administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 12 grams of chlorazene had been dissolved; animal withstood the injection well.

July 22, found dead in the morning; good lesions of rinderpest.

EXPERIMENT 35

Fuga carabao 125.—This animal contracted rinderpest by exposure to sick animals.

July 20, 1917, carabao 125 presented its first rise in temperature, registering, in the afternoon, 40.4° C.

July 21, administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 12 grams of chlorazene had been dissolved.

July 23, bloody diarrhœa; not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 6 grams of chlorazene had been dissolved; also 1,000 cubic centimeters of sodium chloride solution intraperitoneally in which 6 grams of chlorazene had been dissolved.

July 24, bloody diarrhœa; not eating; animal very sick; sunken eyes; discharge from eyes and nostrils; ulcers in mouth, swallowing frequently.

July 25, diarrhœa, not eating; died during the forenoon; good lesions of rinderpest.

EXPERIMENT 36

Fuga bull 4310.—This animal contracted rinderpest by contact with sick animals.

July 21, 1917, bull 4310 presented its first rise in temperature, registering, in the afternoon, 40.2° C.

July 22, administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 9 grams of chlorazene had been dissolved.

July 23, administered intravenously 2,000 cubic centimeters of sodium chloride solution in which 10 grams of chlorazene had been dissolved.

July 26, diarrhœa, not eating; administered intravenously 1,000 cubic centimeters of sodium chloride solution in which 4 grams of chlorazene had been dissolved.

July 27, diarrhœa, not eating.

July 28, found dead in the morning; good lesions of rinderpest.

From the results obtained in experiments 29 to 36, inclusive, it will be noted that chlorazene by the method in which it was administered had no curative effect upon rinderpest.

SALICYLATE OF MERCURY

Salicylate of mercury was used with the idea that it might have a specific action upon the virus of rinderpest. By hypodermic injection rapid and powerful action is obtained, free from gastrointestinal irritation, which has to be considered when treating rinderpest.

In some of the experiments serum was used simultaneously with the salicylate of mercury to try to increase the resistance of the animals toward the disease.

EXPERIMENT 37

Fuga carabao 128.—This animal contracted rinderpest by exposure to sick animals.

July 21, 1917, carabao 128 presented its first rise in temperature, registering, in the afternoon, 39.8° C.

July 24, diarrhœa, not eating; given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of paraffin oil.

July 25, diarrhœa, not eating; given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of paraffin oil.

July 26, diarrhœa, not eating; given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of paraffin oil.

July 27, bloody diarrhœa; not eating; animal very sick.

July 28, found dead in the morning; good lesions of rinderpest.

EXPERIMENT 38

Jolo carabao 98.—This animal contracted rinderpest by exposure to sick animals.

July 24, 1917, carabao 98 presented its first rise in temperature, registering, in the forenoon, 38.9° C.; in the afternoon, 40° C.

July 25, given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of sterile paraffin oil.

July 26, given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of sterile paraffin oil.

July 27, in the forenoon, diarrhœa beginning; in the afternoon, diarrhœa, not eating.

July 28, diarrhœa, not eating.

July 29–31, bloody diarrhœa; not eating; animal very sick.

August 1, bloody diarrhœa; not eating; sunken eyes; discharge from eyes and nostrils; grinding teeth; swallowing frequently; ulcers in mouth; arched back; straining frequently; catchy respiration.

August 2, animal found dead in the morning; good lesions of rinderpest.

EXPERIMENT 39. SERUM AND SALICYLATE OF MERCURY

Fuga carabao 127.—This animal contracted rinderpest by exposure to sick animals.

July 27, 1917, carabao 127 presented its first rise in temperature, registering, in the forenoon, 39.1° C. It was given 300 cubic centimeters of antirinderpest serum subcutaneously and intramuscularly 0.5 gram of salicylate of mercury suspended in 12.5 cubic centimeters of sterile paraffin oil.

July 28, given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 10 cubic centimeters of sterile paraffin oil.

July 29, diarrhœa, not eating; given a deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 10 cubic centimeters of sterile paraffin oil.

July 30, diarrhœa, not eating.

July 31, bloody diarrhœa; not eating; animal very sick.

August 1, bloody diarrhœa; not eating; animal very sick.

August 2, bloody diarrhœa; not eating; died during the forenoon; good lesions of rinderpest.

EXPERIMENT 40. SERUM AND SALICYLATE OF MERCURY

Batanes bull 4317.—This animal contracted rinderpest by exposure to sick animals.

July 28, 1917, bull 4317 presented its first rise in temperature, registering, in the forenoon, 39.2° C.; given 300 cubic centimeters of antirinderpest serum subcutaneously and 0.5 cubic centimeter of sterile paraffin oil intramuscularly.

July 29, given deep intramuscular injection of 0.5 gram of salicylate of mercury suspended in 10 cubic centimeters of sterile paraffin oil; in the afternoon, diarrhœa, eating little.

July 30, diarrhœa, not eating.

July 31, bloody diarrhœa; not eating; animal very sick.

August 1, bloody diarrhœa; not eating; animal died during the forenoon; good lesions of rinderpest.

From the results obtained in experiments 37 and 38 it will be noted that the deep intramuscular injections of salicylate of mercury had no detrimental effect upon the virus of rinderpest. From the results obtained in experiments 39 and 40 it will be noted that the combination of antirinderpest serum and salicylate of mercury had no detrimental effect upon the virus of rinderpest.

ANTIRINDERPEST SERUM

EXPERIMENT 41

Fuga carabao 135.—This animal contracted rinderpest by exposure to sick animals.

July 30, 1917, carabao 135 presented it first rise in temperature, registering, in the forenoon, 38.8° C., and was injected subcutaneously with 300 cubic centimeters of antirinderpest serum.

July 31, not eating.

August 1, not eating.

August 2–3, diarrhœa, not eating.

August 4, diarrhœa, eating little.

August 5–6, bloody diarrhœa; not eating; animal very sick.

August 7, animal found dead in the morning; good lesions of rinderpest.

EXPERIMENT 42

Fuga carabao 134.—This animal contracted rinderpest by exposure to sick animals.

August 10, 1917, carabao 134 presented its first rise in temperature, registering, in the afternoon, 40.1° C.

August 11, given subcutaneously 1,000 cubic centimeters of antirinderpest serum; in the afternoon, diarrhœa starting.

August 12, diarrhœa, not eating.

August 13–14, bloody diarrhœa; not eating; animal very sick.

August 15, animal found dead in the morning; good lesions of rinderpest.

EXPERIMENT 43

Fuga carabao 126.—This animal contracted rinderpest by exposure to sick animals.

August 12, 1917, carabao 126 presented its first rise in temperature, registering, in the forenoon, 39.4° C.; given subcutaneously 1,000 cubic centimeters of antirinderpest serum.

August 14–15, diarrhœa, not eating.

August 16, diarrhœa, not eating; aborted.

August 17, bloody diarrhœa; not eating.

August 18, bloody diarrhœa; not eating.

August 19, bloody diarrhœa; not eating.

August 20, animal found dead in the morning; good lesions of rinderpest.

From the results obtained in experiments 41 to 43, inclusive, it will be noted that antirinderpest serum had no protective effect upon the final outcome of the disease when injected in as large a dosage as 1,000 cubic centimeters.

Antirinderpest serum is very effective when used before the symptoms of rinderpest make their appearance.

It is also beneficial when administered in large quantities to animals that have a high resistance or are infected with an attenuated strain of virus. When handling animals that are highly susceptible, such as are used in the laboratory in experimental work, when such animals are infected with a highly virulent strain of rinderpest, such as is used in the laboratory in carrying on experiments, and when this type of animal presents the first symptoms of the disease, then the administration of antirinderpest serum is of no benefit as a protective or curative agent.

CANABIS INDICA AND SERUM

Canabis indica was used for its antispasmodic, analgesic, and narcotic action and also to stimulate the appetite. It was thought that possibly by the action of the drug and the support it would receive from the antirinderpest serum there might be a chance of the animal developing enough resistance to overcome the disease.

EXPERIMENT 44

Batanes bull 4313.—This animal contracted rinderpest by exposure to sick animals.

July 31, 1917, bull 4313 presented its first rise in temperature, registering, in the afternoon, 40.2° C.

August 1, given subcutaneously 300 cubic centimeters of antirinderpest serum and intravenously 5 cubic centimeters of fluid extract of *Canabis indica.*

August 2, administered intravenously 5 cubic centimeters of fluid extract of *Canabis indica.*

August 3, diarrhœa, not eating; administered intravenously 8 cubic centimeters of fluid extract of *Canabis indica.*

August 4, diarrhœa, eating little; administered intravenously 10 cubic centimeters of fluid extract of *Canabis indica.*

August 5, diarrhœa, eating little; administered intravenously 10 cubic centimeters of fluid extract of *Canabis indica.*

August 6, diarrhœa, eating little; blood and mucus; administered subcutaneously 10 cubic centimeters of fluid extract of *Canabis indica* and given a drench of tannin solution.

August 7, diarrhœa, not eating; administered subcutaneously 10 cubic centimeters of fluid extract of *Canabis indica* and given a drench of tannin solution.

August 8, found dead in the morning; good rinderpest lesions.

EXPERIMENT 45

Batanes bull 4320.—This animal contracted rinderpest by exposure to sick animals.

August 1, 1917, bull 4320 presented its first rise in temperature, registering, in the afternoon, 39.6° C.

August 2, injected subcutaneously 300 cubic centimeters of antirinderpest serum and intravenously 5 cubic centimeters of fluid extract of *Canabis indica.*

August 3, diarrhœa, not eating; given intravenously 5 cubic centimeters of fluid extract of *Canabis indica.*

August 4, diarrhœa, eating little; given intravenously 10 cubic centimeters of fluid extract of *Canabis indica.*

August 5, diarrhœa, eating little; given intravenously 10 cubic centimeters of fluid extract of *Canabis indica.*

August 6, diarrhœa, eating little; given intravenously 10 cubic centimeters of fluid extract of *Canabis indica.*

August 7, bloody diarrhœa; not eating; given subcutaneously 10 cubic centimeters of fluid extract of *Canabis indica* and given a drench of tannin solution; animal very sick.

August 8, animal found dead in the morning; good lesions of rinderpest.

EXPERIMENT 46

Fuga bull 4323.—This animal contracted rinderpest by exposure to sick animals.

August 4, 1917, bull 4323 presented its first rise in temperature, registering, in the forenoon, 39.2° C.

August 5, diarrhœa; administered subcutaneously 500 cubic centimeters of antirinderpest serum and intravenously 5 cubic centimeters of fluid extract of *Canabis indica.*

August 6, diarrhœa, not eating; straining; very sick; administered intravenously 10 cubic centimeters of fluid extract of *Canabis indica* and given a drench of tannin solution.

August 7, bloody diarrhœa; not eating; straining; very sick; given intravenously 10 cubic centimeters of fluid extract of *Canabis indica;* given a drench of tannin solution.

August 8, animal found dead in the morning; good lesions of rinderpest.

From the results obtained in experiments 44 to 46, inclusive, it will be noticed that the administration of fluid extract of *Canabis indica* and antirinderpest serum had no effect upon the final outcome of the disease. The animals used in experiments 44 and 45 continued to eat for a much longer time than is usually the case in a fatal attack of rinderpest, and in this respect the *Canabis indica* helped them. They also did not develop ulcers in their mouths until the day before death.

MEDICINAL METHYLENE BLUE

EXPERIMENT 47

Fuga bull 4324.—This animal contracted rinderpest by exposure to sick animals.

August 8, 1917, bull 4324 presented its first rise in temperature, registering 39.9° C.

August 9, administered intravenously 800 cubic centimeters of sodium chloride solution in which 1 gram of medicinal methylene blue (Merck) had been dissolved; in the afternoon diarrhœa beginning.

August 10, bloody diarrhœa; not eating; administered intravenously 500 cubic centimeters of sodium chloride solution in which 0.5 gram of medicinal methylene blue had been dissolved.

August 11, bloody diarrhœa; not eating; animal very sick; administered intravenously 500 cubic centimeters of sodium chloride solution in which 0.8 gram of medicinal methylene blue had been dissolved.

August 12, animal found dead in the morning; good lesions of rinderpest.

From the results obtained in experiments 2 and 47 it will be noticed that medicinal methylene blue has apparently no detrimental effect upon the virus of rinderpest when administered either subcutaneously or intravenously.

MISCELLANEOUS EXPERIMENTS

The data on the following experiments cannot be located, but I have the results of these experiments in mind.

1. During 1913 a small Batanes bull suffering from an attack of rinderpest was injected intraperitoneally with quinine sulphate that had been dissolved in acidulated sodium chloride solution. This animal recovered from the disease. Without doubt the animal would have made a recovery without any

treatment, when the results of further experiments with quinine sulphate are considered.

2. During 1913 two Batanes bulls suffering from rinderpest were given subcutaneously injections of camphorated oil, which is frequently prescribed as a circulatory stimulant in septicæmia. Both of these animals died of rinderpest.

3. In the early part of 1914 two animals that were suffering from rinderpest were treated with fluid extract of gentian and fluid extract of nux vomica. These drugs were administered with the idea of keeping the circulation and appetite toned up. Both animals died of rinderpest, the drugs having practically no effect upon them, as both animals developed inappetence and diarrhœa and died in the usual length of time noticed in severe cases of rinderpest.

4. During the early part of 1914 a bull suffering from rinderpest was drenched with dilute alcohol administered at short intervals. This animal developed all the symptoms of rinderpest and died of that disease in the usual length of time.

5. During 1912 several animals were treated with castor oil, and all of them developed the usual symptoms and lesions of rinderpest and died of that disease.

FIELD NOTES

Dr. Stanton Youngberg, chief veterinarian, Bureau of Agriculture, and the several veterinarians in charge of the immunization stations in the provinces have been using strychnine, nitroglycerin, and echinacoid on animals that have a severe reaction while passing through the immunization. (Simultaneous method, receiving an infecting dose of virulent rinderpest blood and a supposedly protecting dose of antirinderpest serum on the same day or within one or two days of each other.)

These workers find that all three of the above-mentioned drugs prolong the life of animals by their stimulating effect and in many instances seem to sustain life long enough for the animal to develop sufficient antibodies to combat the disease and in this way make a recovery. They find that when using strychnine great care has to be taken in not stopping the use of the drug too suddenly, as its action is very transient and if not administered at short intervals the animal is apt to suffer a collapse and die suddenly.

With nitroglycerin and echinacoid the stimulating effect is of longer duration and collapse is not so frequently noticed.

Although these drugs are practically useless for animals that contract rinderpest in the usual way and have not previously

received a protecting dose of serum, the results indicate that they may be used on animals that have severe reactions while being immunized.

CONCLUSIONS

1. From the results of the 47 experiments in which drugs and serum were used in treating animals sick with rinderpest, it will be noticed that but one animal, carabao 3182, experiment 20, recovered from the disease and that animals of subsequent experiments (21 to 26, inclusive), treated similarly to carabao 3182, succumbed to the disease, which proves conclusively that carabao 3182 would have recovered as readily without any treatment.

2. From the result obtained in No. 1 of the miscellaneous experiments it is evident that this animal would have made a recovery without any treatment, when the results of experiments 7 to 10, inclusive, are considered. The animals in these experiments were treated in a similar manner, and all of them succumbed to the disease.

3. It will be noticed that over fifty animals were experimented upon with the various drugs mentioned and that but two animals recovered from the disease, which is positive proof that the drugs used and administered as they were had no curative power for an animal suffering from rinderpest.

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PROCEEDINGS OF THE MANILA MEDICAL SOCIETY

REGULAR MONTHLY MEETING, DECEMBER 3, 1917

MINUTES OF THE MANILA MEDICAL SOCIETY

The regular monthly meeting of the Manila Medical Society was held at the College of Medicine and Surgery on Monday evening, December 3, 1917. In the absence of the president and the secretary, the meeting was called to order by Dr. B. C. Crowell, president of the Philippine Islands Medical Association. On motion duly made and seconded, there being no objection, Doctor Crowell took the chair and appointed Dr. R. B. Gibson as secretary pro tempore.

Doctor Crowell presented the name of Dr. Emiliano M. Panis for membership in the Manila Medical Society. On motion, duly seconded and carried, Doctor Panis's application was referred to the council for final action.

There being no other business, the scientific program for the evening was taken up.

R. B. GIBSON,
Secretary pro tempore,
Manila Medical Society.

SCIENTIFIC PROGRAM

ON PHILIPPINE MEDICINAL PLANTS

By DR. LEON M. GUERRERO

The flora in the Philippines are rich in pharmacological products, the systematic pharmacological and chemical investigation of which deserves attention. Many plant preparations used by the natives or empirically prescribed by quacks have some therapeutic value. Among these may be mentioned *Alstonia scholaris* for malaria and which may serve perhaps also as a cardiac remedy; *Lunasia amara* employed as gastric sedative, but which has been found to contain an alkaloid producing nonspinal convulsions; the seeds of *Quisqualis indica,* known to the native Filipinos as a vermifuge; *Tylophora brevipes,* similar to *Tylophora asthmatica* of India, which contains an alkaloid *tylophorine* and which is popularly used as an emetic and also as an antidysenteric, expectorant, and emmenagogue; *Tinospora*

reticulata, used for malaria and probably containing berberine; and several species of strophanthus, the lethal dose of which is not unknown to the natives.

SERUM THERAPY OF BACILLARY DYSENTERY

By Dr. Pedro T. Lantin

Specific serum therapy for bacillary dysentery has until the last few years fallen into disrepute. The work of later investigators indicates that the serum therapy of bacillary dysentery is an effective means of checking the disease. The present paper gives the results of the treatment of 20 cases of bacillary dysentery treated with antidysentery serum. Of these 20 cases, 5 were treated medicinally and with intramuscular injections of serum, 1 death occurring; 6 were treated with serum intramuscularly and per rectum, with no deaths; 3 cases were treated with serum per rectum, with no deaths; and finally 3 cases were treated intravenously with serum, with no deaths. The majority of the cases were severe; the single case that died had been admitted to the hospital in a state of collapse. Administration per rectum was done with the patient in the knee-chest position, 30 to 50 cubic centimeters being given daily, preceded a half hour earlier by sodium carbonate (1.5 per cent) to cleanse the bowels and 60 cubic centimeters of starch-solution enema containing 10 drops of tincture of opium. Twenty cubic centimeters of serum were used twice a day when given intramuscularly, and 10 cubic centimeters every other day, intravenously with several hours previous administration of 1 cubic centimeter hypodermically to avoid anaphylaxis. The serum treatments were followed by a prompt reduction in the number of stools and a diminution of the fever. The per rectum administration of serum in the cases so treated brought about a marked alleviation of the local symptoms; it may be used in mild cases or in conjunction with intramuscular or intravenous injections. In view of the facts established in the literature, successful results should follow the use of bacillary dysentery serum in the Philippine Islands as evidenced in the cases reported by the writer.

DISCUSSION

Doctor Schöbl reviewed the types of dysentery bacilli and the methods of differentiating these and said that the antitoxic serum used was prepared according to Doerr with cultures of the Shiga-Kruse group. Doctor de la Paz discussed some phar-

macological aspects of the methods used in the per rectum administration of the serum, stating that the lessening of the number of stools, because of the morphine given, must be taken into consideration if this is to be considered one of the criteria of improvement as the result of the serum therapy. Doctor Calderon reported that he had experienced little success with antidysentery serum, but thought that the freshly prepared local product might be more effective. Doctor Albert stated that he has practically failed in treating dysentery in children with serum, but most of his cases were in a collapsed and dying condition when admitted to the hospital.

REMOTE MANIFESTATIONS OF FOCAL DENTAL INFECTION, WITH CASE REPORTS

By Dr. R. Fernandez

The writer emphasized the work of the last seven years on the importance of focal chronic dental infections to such conditions as arthritis, neuritis, gastritis, leucæmia, etc. He spoke of the local treatment of the abscess, the use of autogenous vaccines, and particularly the diagnosis by means of the Röntgen ray. The methods employed require 5 exposures by the extraoscular method and 12 by the intraoscular; the former is to be preferred. Skiagrams showing focal dental lesions and case histories were presented, the results of the treatment being in full accord with recent published observations.

DISCUSSION

Doctor Crowell pointed out that while attention to the teeth as a source of obscure infections is important, we must consider also the appendix, other parts of the intestines, the gall bladder, the stomach, deflected septum, and hypertrophied turbinates of the nose, the ears, and the genito-urinary organs. Doctor Ottofy quoted an article by Willoughby D. Miller, an American dentist in Berlin, written twenty-seven years ago, in which the significance of focal dental infections was pointed out; he reviewed the late development of this study in the United States and emphasized the necessity of prophylaxis, proper bridge work, and the needless extraction of teeth, many of which may be saved for the patient.

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